hydroxide was added, a result which is intriguingly explicable (but unestablished) in terms of fragmentation followed by subsequent cyclization in the weakly acidic medium.

(23) J. A. Marshall and G. L. Bundy, *Chem Commun* 854 (1967).

(24) Several interconversions and cross-checks were carried out in order to make sure that at no stage was the trans,syn,trans stereochemistry of the tricyclic compounds changed. Exemplary is the thioketalization of **25** and subsequent desulfurization to authentic *trans,syn,trans*-perhydroanthracene, the structure of which rests on X-ray evidence. See S. Bog, O. Hassel, and E. H. Vihovde, *Acta Chem. Scand.*, **7**, 1308 (1953).

(25) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N.Y., 1967.

(26) See R. K. Hill, J. G. Martin, and W. H. Storch, *J. Amer. Chem. Soc.*, **83**, 4006 (1961).

(27) W. S. Johnson, V. J. Bauer, J. L. Margrave, M. A. Frisch, L. H. Dreger, and W. N. Hubbard, *J. Amer. Chem. Soc.*, **83**, 606 (1961).

Regioselective [4 + 2] and [2 + 2] Cycloadditions of 1-Azirines to Heterocumulenes. Formation and Rearrangements of the Cycloadducts

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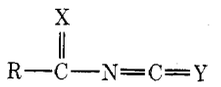
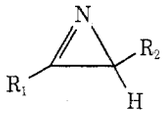
The cycloaddition of 1-azirines to some heterocumulenes is presented. The thermal reaction of representative 1-azirines (**4**) to thiobenzoyl isocyanate (**2**) results in exclusive [4 + 2] cycloaddition. The regiospecificity of the reaction was confirmed by hydrolysis of the cycloadducts **5** to the ureas **6**. Controlled thermolysis of **5a** results in the formation of a novel seven-membered-ring system, a thiadiazepinone (**7**). Compound **7** undergoes a sulfur extrusion reaction thermally to give a pyrimidine ring system (**8**). Benzoyl isocyanate (**1**) also gave [4 + 2] cycloaddition products (**9**). Benzoyl isothiocyanate (**3**), however, gave products (**12**) resulting apparently from a regiospecific [2 + 2] cycloaddition about the C=S bond. The nature of the transition state for the initial [2 + 2] addition is discussed. Structural identification came from mass spectral and nmr studies, particularly ^{13}C nmr.

Heterocumulenes containing a carbonyl or related unsaturation adjacent to the cumulative bonds such as **1**, **2** and **3**, offer the possibility of entry into complex heterocyclic



1, R = Ph; X = O; Y = O
2, R = Ph; X = S; Y = O
3, R = Ph; X = O; Y = S

systems through thermal symmetry-allowed [$_\pi4_s$ + $_\pi2_s$] or [$_\pi2_s$ + $_\pi2_a$] pericyclic reactions. The small ring nitrogen heterocycle, 1-azirine (**4**), may participate as a component in



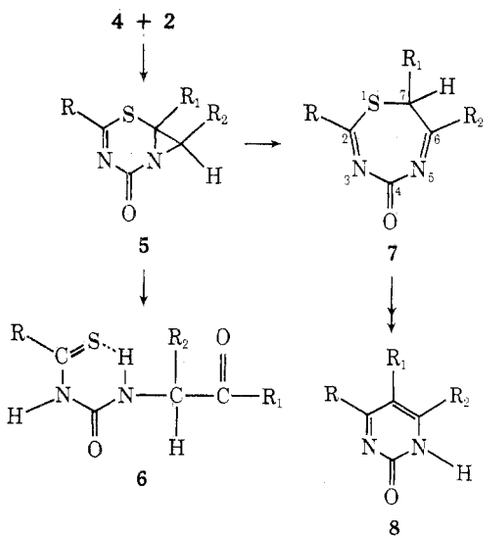
4a, R_1 = Ph; R_2 = Ph
b, R_1 = Ph; R_2 = CH_3
c, R_1 = Ph; R_2 = H

these cycloadditions by utilizing its reactive π bond.[1-4] The possibility of regioselectivity resulting from the inherent polarization in both components enhances the complexity of these reactions. We wish to report on such cycloadditions and to provide evidence that minor structural changes in the heterocumulenes can produce gross changes, not only in the preferred mechanistic pathway for the formation of the adducts, but also in the thermal stability of the final products. A brief announcement of some of our results was made earlier.[11]

Results and Discussion

Thiobenzoyl isocyanate (**2**) can be generated from 2-phenylthiazoline-4,5-dione by thermal extrusion of carbon monoxide.[5-8] When a solution of freshly generated **2** in *p*-xylene was treated with 2,3-diphenyl-1-azirine (**4a**)[9,10] at room temperature for 12 hr, and the reaction mixture after solvent removal was subjected to preparative layer chromatography, a white crystalline compound was obtained, mp 154–155°.[11] Its mass spectral parent ion (*m/e* 356) and fragmentation pattern established the presence of the azirine and thiobenzoyl isocyanate moieties within the structure and that the yield of adduct was high (85%). At least three possibilities exist for the mode of addition:[12] (i) $_\pi4_s$ + $_\pi2_s$ cycloaddition, (ii) $_\pi2_s$ + $_\pi2_a$ adduction, (iii) initial nucleophilic attack by the lone pair of the azirine nitrogen on the highly reactive electrophilic carbon of the carbonyl of the isocyanate and subsequent 1,3-bond scission and cyclization in one or more ways. That the product was actually the result of an exclusive [$_\pi4_s$ + $_\pi2_s$] cycloaddition (**5a**) came from its PFT carbon-13 nmr spectral evidence. The aziridine carbons appeared at δ 53.31 and 56.60, the carbonyl carbon at 173.46, and the imine carbon at 162.94.

The question of the direction or regiospecificity of the cycloaddition and further substantiation of structure was provided in an elegant way by the acid-catalyzed hydrolysis of **5a** to the urea **6a**, yellow plates, mp 199–201°. Dramatic



proof for this mode of ring opening was provided by the observation of three different carbonyl-type carbons (>C=O, N—C(=O)—N, C=S) as suggested by chemical shift correlations in the ^{13}C nmr spectrum. Further confirmation

was provided by the ^1H nmr spectrum of **6a** which showed the two urea N–H absorptions at δ 9.87 (singlet) and 10.47 (doublet, J = 6.9 Hz). A remarkable observation in the ^1H nmr study was the very slow rate of deuterium exchange of the N–H at δ 10.47 suggesting the presence of intramolecular hydrogen bonding. That this was indeed the case was shown by the diagnostic infrared shift of the hydrogen bonded N–H to 2400 cm^{-1} on deuteration.[13,14]

When the cycloadduct **5a** was subjected to thermolysis at 80°, a yellow crystalline compound, mp 165–167°, was isolated after chromatographic purification in 67% yield. Its 70-eV mass spectrum suggested that a rearrangement without fragmentation had occurred. The infrared spectrum showed no N–H absorption but peaks at 1725 and 1650 cm^{-1}. Its ^{13}C nmr spectrum (in $CDCl_3$) suggested the structure **7a** with δ 91.67 (C-7), singlets between 127.44 and 135.42 (phenyl carbons), 139.42 (C-6), 162.94 (C-2), 194.12 (C-4).

Prolonged thermolysis of **5a** at higher temperatures (110°) resulted in the removal of elemental sulfur and the eventual formation of a pyrimidone **8a.** That **7a** was indeed the intermediate in this sulfur extrusion reaction was confirmed not only by its isolation from the reaction mixture but also by its actual quantitative conversion to **8a** at 110°.

The differences in the stability of the cycloadducts derived from the three azirines bear consideration. The reactivity toward hydrolytic cleavage is in the direction **5a** < **5b** < **5c.** Compound **5c** undergoes hydrolysis even on silica gel columns whereas compound **5a** has to be heated at 55° for at least several hours. Whereas this acid-catalyzed hydrolysis proceeds quantitatively for **5b** and **5c** the lower yield (49%) in the case of **5a** is a reflection of the competitive ring opening reaction to **7a.** This rearrangement reaction is relatively unimportant for **5b** and **5c** even at elevated temperatures (138°, *p*-xylene reflux). Thermally **5b** and **5c** are much more stable than **5a.**

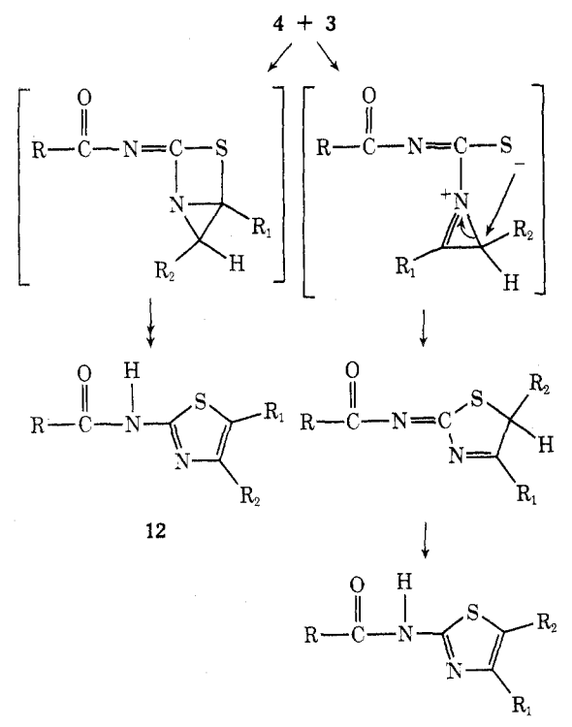
Our results with **2** prompted the investigation of the reaction of benzoyl isocyanate (**1**)[8] with 1-azirines (**4**). We discovered that the behavior of benzoyl isocyanate toward **4** paralleled those of thiobenzoyl isocyanate and [4 + 2] cycloaddition products **9** were isolated.[15] These compounds

Table I
Thermal Decomposition of 0.572 *M* Cycloadduct (9b) at 70°

Time, hr	*M* concn of **9b**	Dec, %
0	0.572	0
0.5	0.482	15.8
1.0	0.431	24.6
1.5	0.391	31.6
2.0	0.361	36.9
2.5	0.340	40.5
4.5	0.301	47.4
6.5	0.281	50.8
8.0	0.274	51.7
16.0	0.274	51.7

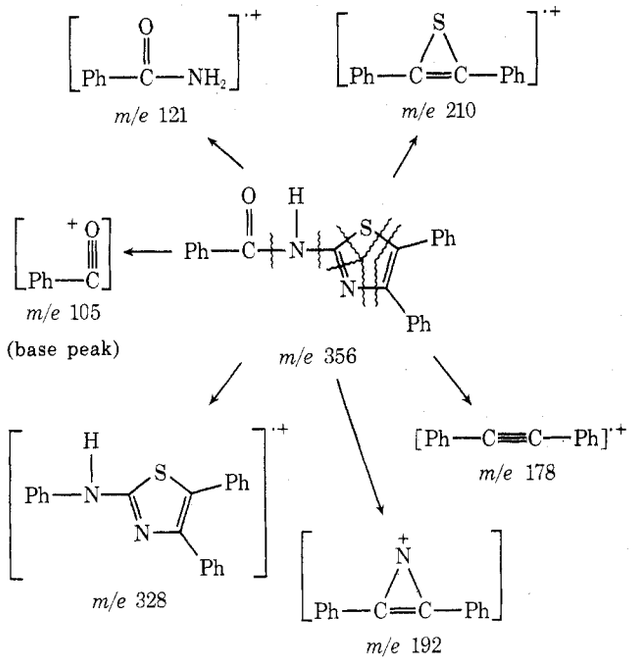
could be hydrolyzed to the ureas **10** under acid-catalyzed conditions. Thermolysis to **11** was not observed. At 70° a clean retro [4 + 2] pericyclic reaction took place and equilibrium was attained after 8 hr with $K = 3.24 \pm 0.20 \times 10^{-1}$.

Benzoyl isothiocyanate (**3**) can be prepared by the reaction of benzoyl chloride and lead thiocyanate.[16,17] A literature search revealed that only a limited amount of work had been done in the area of cycloadditions to **3.** We attempted the reaction of **3** with 1-azirines, not only to establish its preferred mode of addition, but also as a comparison with the behavior of **1** and **2** where exclusive [4 + 2] cycloaddition was observed. Thus, when 2,3-diphenyl-1-azirine (**4a**) was treated with benzoyl isothiocyanate (**3**) in refluxing benzene for 12 hr, preparative layer chromatography gave a white crystalline cycloadduct in 68% conversion, mp 143–144°. Mass spectral data and elemental analysis were consistent with the molecular formula $C_{22}H_{16}N_2OS$. The infrared spectrum showed diagnostic absorptions at 3270, 1675, and 1550 cm^{-1}. Its ^1H nmr spectrum (in $CDCl_3$) showed aromatic absorptions and a broad singlet (1 H) at δ 11.15 which underwent rapid exchange with D_2O. The PFT ^{13}C nmr spectrum (in $CDCl_3$)[27] showed singlets in the phenyl carbon region and resonances at δ 144.51, 157.46, and 165.33. This inconsistency in the nmr spectral data with a [4 + 2] cycloadduct was also apparent in the mass spectrum. Collectively, the data were consistent with benzamide bearing a thiazole ring system on the amide nitrogen. Two plausible structures are **12** and **13.** Compound **12** is

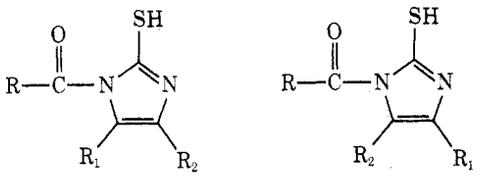


the eventual result of a $[_\pi 2_s + _\pi 2_a]$ cycloaddition and hydrogen shift(s). Compound **13** results from initial nucleophilic attack, 1,3-bond scission and cylization, and a 1,5-sigmatropic hydrogen shift. Both structures are consistent with the mass spectral data, *e.g.*, for **12a**[18] (Scheme I).

Scheme I



Mass spectral data, however, rules out structures **14** and **15**, the result of addition across the C=N bond of **3**.



14 **15**

Final structural confirmation came from the ^{1}H nmr spectrum of **12c** which showed the 4-H absorption as a singlet at δ 7.08. From comparison of a number of known thiazole derivatives it is clear that this absorption would be about 0.5 ppm upfield if the structure was **13c**.[19-21]

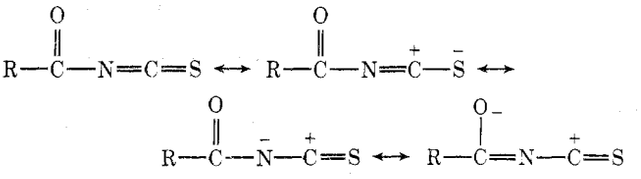
The marked difference in behavior between the exclusive [4 + 2] cycloaddition observed for benzoyl isocyanate (**1**) and thiobenzoyl isocyanate (**2**) and the apparent [2 + 2] cycloaddition in a regiospecific manner to the C=S bond of **3** requires explanation. Orbital symmetry analysis[12,22] reveals a possible concerted [$_\pi 2_s$ + $_\pi 2_a$] pathway but does not explain why the replacement of O by S produces such a marked change in mechanism. A striking clue to the nature of the transition state came from solvent polarity studies with **4c** at 75° (Table II) which showed a dramatic increase

Table II
Reaction of 2-Phenyl-1-azirine (4c) with Benzoyl Isothiocyanate at 75°

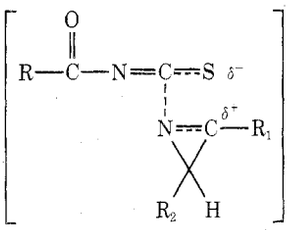
Solvent	Dielectric constant	Reaction time, hr	% yield of **12c**
Benzene	2.3	2	13.4 ± 1.5
Ethyl acetate	6.0	2	19.3 ± 1.5
Nitrobenzene	34.8	2	42.7 ± 1.5

in product yield with increase in the dielectric constant of the solvent. We interpret this solvent dependency as reflecting the presence of a polar transition state in the pathway to the formation of the initial cycloadduct. The polarization of **3** (Scheme II) is similar to **1** except for the greater

Scheme II



ability of sulfur to stabilize a negative charge.[17] A dipolar transition state such as **16** could conceivably account not



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only for the solvent dependency but also for the marked difference in behavior between **1**, **2**, and **3**. Whether such a transition state would transform into a relatively stable dipolar intermediate[23] so as to favor a two-step combination is not known.

Experimental Section

General. All melting points are uncorrected. The ir spectra were recorded on a Beckman IR-20A. The nmr spectra were determined at 60 MHz with a Varian A-60 nmr spectrometer with TMS as the internal reference and with a Bruker HX-90E PFT nmr spectrometer interfaced with a Nicolet 1080 computer and disk unit. The mass spectra were obtained on a Hitachi RMU-6E mass spectrometer using direct inlet and an ionization energy of 70 eV. Elemental analyses were performed by the University of Iowa Microanalytical Service.

2,3-Diphenyl-1-azirine (**4a**) and 2-phenyl-1-azirine (**4c**) were prepared by a modification of the literature method.[9,10] 3-Methyl-2-phenyl-1-azirine (**4b**) was prepared by the method of Nair.[24] 2-Phenylthiazoline-4,5-dione was prepared by the method of Goerdeler, *et al.*[5,7,25] Thiobenzoyl isocyanate was generated by thermolysis of 2-phenylthiazoline-4,5-dione in *p*-xylene at 120° for 5 min and used *in situ*. Benzoyl isocyanate was prepared from benzamide and oxalyl chloride by established methods.[8,26] Benzoyl isothiocyanate can be obtained from the reaction of benzoyl chloride and lead thiocyanate.[16]

Reaction of 2,3-Diphenyl-1-azirine (4a) with Thiobenzoyl Isocyanate (2). A solution of thiobenzoyl isocyanate (**2**) in *p*-xylene generated from 2.865 g (15 mmol) of 2-phenylthiazoline-4,5-dione was treated at 25° with 2.42 g (12.5 mmol) of 2,3-diphenyl-1-azirine (**4a**) and the reaction mixture was stirred for 4 hr at 25°. The precipitated material was filtered off and chromatographed using a silica gel column. The product was eluted with ether. Crystallization from ether gave 3.673 g (85% yield based on 1-azirine) of **5a** as white rectangular crystals: mp 154–155°; ir ν_{max} (Nujol) 1720 (C=O), 1550 (C=N) cm^{-1}; ^{1}H nmr δ_{TMS} ($CDCl_3$) 4.46 (s, 1 H), 7.10–8.17 (m, 15 H); ^{13}C nmr δ_{TMS} ($CDCl_3$) 53.31, 56.60, 127.55, 127.82, 128.46, 128.95, 129.22, 129.38, 129.54, 132.94, 134.18, 135.48, 136.93, 162.94, 173.46; mass spectrum *m/e* 356 (M^+), 324 (M^+ − S), 296 (M^+ − S–CO), 253 (M^+ − PhCN), 193 (azirine), 163 (isocyanate), 103 (PhCN).

Anal. Calcd for $C_{22}H_{16}N_2OS$: C, 74.13; H, 4.52; N, 7.86. Found: C, 73.89; H, 4.47; N, 8.05.

Reaction of 3-Methyl-2-phenyl-1-azirine (4b) with Thiobenzoyl Isocyanate (2). The azirine (**4b**) (0.524 g, 4 mmol) was treated with thiobenzoyl isocyanate (**2**) as described above and the reaction mixture was stirred at 25° for 24 hr. The product was separated by column chromatography on silica gel with 50% ether–pentane as the eluent. Crystallization from ether–pentane gave colorless rectangular crystals of **5b** (0.841 g, 72%): mp 96–98°; ir ν_{max} (Nujol) 1719 (C=O), 1560 (C=N) cm^{-1}; ^{1}H nmr δ_{TMS} ($CDCl_3$) 1.15 (d, J = 5.8 Hz, 3 H), 3.42 (q, J = 5.8 Hz, 1 H), 7.18–8.15 (m, 10 H); ^{13}C nmr δ_{TMS} ($CDCl_3$) 14.73, 47.85, 54.16, 127.14, 128.76, 129.35, 134.15, 135.07, 137.39, 171.70, 173.15; mass spec-

trum *m/e* 251 (M^+ − HNCO), 191 (M^+ − PhCN), 163 (isocyanate), 148 ($Ph(C_2S)CH_3$), 131 (azirine), 103 (PhCN) (product partly rearranged under operating conditions).

Anal. Calcd for $C_{17}H_{14}N_2OS$: C, 69.36; H, 4.79; N, 9.52. Found: C, 69.50; H, 4.90; N, 9.24.

Reaction of 2-Phenyl-1-azirine (4c) with Thiobenzoyl Isocyanate (2). The azirine (**4c**) (0.351 g, 3 mmol) was treated with **2** and chromatographed as described above to give 0.172 g (20%) of **5c** as colorless rectangular crystals: mp 128–129°; ir ν_{max} (Nujol) 1710 (C=O), 1560 (C=N) cm^{-1}; ^1H nmr δ_{TMS} ($CDCl_3$) 2.80 (s, 1 H), 3.13 (s, 1 H), 7.22–8.20 (m, 10 H); mass spectrum *m/e* 280 (M^+), 248 (M^+ − S), 177 (M − PhCN), 163 (isocyanate), 117 (azirine), 103 (PhCN).

Anal. Calcd for $C_{16}H_{12}N_2OS$: C, 68.55; H, 4.32; N, 9.99. Found: C, 68.21; H, 4.21; N, 9.99.

When the silica gel column was eluted with CH_2Cl_2, 0.344 g (38.5%) of **6c** was obtained as yellow needles: mp 166–167°; ir ν_{max} (Nujol) 3240, 3120 (N–H), 1690 (br) (C=O), 1535 cm^{-1}; ^1H nmr δ_{TMS} ($CDCl_3$) 4.87 (d, J = 5.0 Hz, 2 H), 7.25–8.17 (m, 10 H), 10.06 (s, br, 1 H, exchanges in D_2O), 10.69 (t, J = 5.0 Hz, 1 H, very slow D_2O exchange); ^{13}C nmr δ_{TMS} ($CDCl_3$) 47.63, 127.03, 128.06, 128.65, 128.97, 132.16, 134.04, 134.58, 154.00, 193.06, 200.93; mass spectrum *m/e* 298 (M^+), 264 (M^+ − H_2S), 193 (M^+ − PhCO), 177 (M^+ − PhCS), 161 ($PhCOCH_2NCO$), 137 ($PhCSNH_2$), 121 (PhCS), 105 (PhCO).

Anal. Calcd for $C_{16}H_{14}N_2O_2S$: C, 64.40; H, 4.71; N, 9.39. Found: C, 64.38; H, 4.81; N, 9.21.

Thermolysis of Cycloadduct (5a) at 80°. Formation and Isolation of Thiadiazepinone (7a). A solution of 0.250 g (0.7 mmol) of **5a** in 10 ml of benzene was heated under reflux for 6 hr. The solvent was removed and the residue was chromatographed on preparative layer silica gel PF_{254} plates with 50% ether–pentane as the developing solvent. The thiadiazepinone (**7a**) crystallized from ether–pentane as yellow prisms (0.168 g, 67%): mp 165–167°; ir ν_{max} (Nujol) 1725 (C=O), 1650 (C=N) cm^{-1}; ^1H nmr δ_{TMS} ($CDCl_3$) 7.22–8.40 (m, 15 H), 8.62 (s, 1 H); ^{13}C nmr δ_{TMS} ($CDCl_3$) 91.67, 127.44, 128.84, 129.22, 132.02, 135.42, 139.42, 162.94, 194.12; mass spectrum *m/e* 356 (M^+), 324 (M^+ − S), 296 (M^+ − S–CO), 253 (M^+ − PhCN), 193 (azirine), 163 (isocyanate), 121 (PhCS), 103 (PhCN).

Anal. Calcd for $C_{22}H_{16}N_2OS$: C, 74.13; H, 4.52; N, 7.86. Found: C, 73.93, H, 4.43; N, 7.71.

Thermolysis of Cycloadduct (5a) at 110°. Isolation of Pyrimidone (8a). A solution of 0.965 g (2.6 mmol) of **5a** in 20 ml of toluene was heated under reflux for 24 hr. The pyrimidone (**8a**) crystallized directly out of the reaction mixture as yellow needles (0.475 g, 54%): mp 274–278°; ir ν_{max} (Nujol) 3340 (br, N–H), 1645 (C=O), 1590 (C=N) cm^{-1}; ^1H nmr δ_{TMS} (CF_3CO_2H) 7.10–8.20 (m, 16 H); mass spectrum *m/e* 324 (M^+), 296 (M^+ − CO), 193 (azirine), 103 (PhCN).

Anal. Calcd for $C_{22}H_{16}N_2O$: C, 81.46; H, 4.94; N, 8.64. Found: C, 81.25; H, 5.22; N, 8.33.

Thermolysis of Thiadiazepinone (7a). Isolation of Pyrimidone (8a). A solution of 0.08 g (0.225 mmol) of **7a** in 15 ml of toluene was heated under reflux for 24 hr. The solvent was then removed and the residue was crystallized from dichloromethane–ether to give **8a** as yellow needles (0.063 g, 86.5%): mp 274–278°.

Hydrolysis of Cycloadduct (5a). A suspension of **5a** (0.200 g, 0.56 mmol) in 15 ml of 1 *M* HCl was stirred at 55° for 24 hr. The yellow solid formed was filtered, washed with water, and purified by preparative plates (silica gel PF_{254}) using ether as the developing solvent. The urea **6a** crystallized from ethanol as yellow plates (0.103 g, 49%): mp 199–201°; ir ν_{max} (Nujol) 3240, 3105 (NH), 1700 (C=O), 1690 (C=O) cm^{-1}; ^1H nmr δ_{TMS} ($CDCl_3$) 6.58 (d, J = 6.9 Hz, 1 H), 6.8–8.17 (m, 15 H), 9.87 (s, br, 1 H, exchanges with D_2O), 10.47 (d, br, J = 6.9 Hz, 1 H, very slow exchange with D_2O); ^{13}C nmr δ_{TMS} ($CDCl_3$) 59.44, 127.41, 128.16, 128.81, 131.40, 133.72, 134.04, 136.31, 136.46, 141.97, 152.16, 195.11, 202.17; mass spectrum *m/e* 374 (M^+), 340 (M^+ − H_2S), 269 (M^+ − PhCO), 253 (M^+ − PhCS), 163 (PhCSNCO).

Anal. Calcd for $C_{22}H_{18}N_2O_2S$: C, 70.57; H, 4.85; N, 7.48. Found: C, 70.69; H, 4.90; N, 7.36.

Hydrolysis of cycloadduct (5b) (0.200 g, 0.68 mmol) with 1 *M* HCl gave the urea **6b** (0.195 g, 92%): mp 136–138°; ir ν_{max} (Nujol) 3240, 3145 (NH), 1702 (br, C=O) cm^{-1}; ^1H nmr δ_{TMS} ($CDCl_3$) 1.51 (d, J = 7.0 Hz, 3 H), 5.53 (m, J = 6.9 Hz, 7.0 Hz, 1 H), 7.12–8.16 (m, 10 H), 10.39 (s, br, 1 H, exchanges with D_2O), 10.78 (d, br, J = 6.9 Hz, 1 H, very slow exchange with D_2O); ^{13}C nmr δ_{TMS} ($CDCl_3$) 19.31, 51.89, 127.14, 128.49, 128.76, 130.59, 132.05, 133.88, 142.24, 153.63, 197.86, 201.15; mass spectrum *m/e* 312 (M^+), 278 (M^+ − H_2S), 207 (M^+ − PhCO), 191 (M^+ − PhCS), 163 (PhCSNCO).

Anal. Calcd for $C_{17}H_{16}N_2O_2S$: C, 65.36; H, 5.16; N, 8.97. Found: C, 65.21; H, 5.21; N, 8.60.

Reaction of 3-Methyl-2-phenyl-1-azirine (4b) with Benzoyl Isocyanate (1). To a solution of 0.588 g (4 mmol) of benzoyl isocyanate in 5 ml of benzene was added 0.524 g (4 mmol) of the azirine (**4b**) in 5 ml of benzene. The reaction mixture was stirred at 25° for 20 hr and then chromatographed on a silica gel column using 50% ether–pentane as the eluting solvent for the product. The cycloadduct (**9b**) crystallized from ether-pentane as white needles (0.510 g, 45.5%): mp 111–113°; ir ν_{max} (Nujol) 1730 (C=O), 1610 (C=N) cm^{-1}; ^1H nmr δ_{TMS} ($CDCl_3$) 1.17 (d, J = 5.8 Hz, 3 H), 3.16 (q, J = 5.8 Hz, 1 H), 7.22–8.25 (m, 10 H); ^{13}C nmr δ_{TMS} ($CDCl_3$) 13.59, 44.45, 78.86, 127.14, 128.65, 129.19, 129.52, 129.73, 132.32, 134.48, 163.39, 167.17; mass spectrum *m/e* 147 (PhCONCO), 131 (azirine), 105 (PhCO), 103 (PhCN).

Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.36; H, 5.07; N, 10.06. Found: C, 73.07; H, 4.98; N, 10.21.

Reaction of 2-Phenyl-1-azirine (4c) with Benzoyl Isocyanate (1). The azirine (**4c**) (0.588 g, 4 mmol) was treated with 1 in benzene at 25° for 7 hr. Subsequent column chromatography resulted in hydrolysis of the cycloadduct **9c** to the urea **10c.** The urea **10c** was eluted from the column with CH_2Cl_2 and crystallized from ethanol as white needles (0.467 g, 40%): mp 146–147°; ν_{max} (Nujol) 3250 (NH), 1710 (C=O), 1690 (C=O), 1545 (amide II band); ^1H nmr δ_{TMS} ($CDCl_3$) 4.82 (d, J = 5.0 Hz, 2H), 7.16–8.18 (m, 10 H), 9.59 (d, br, J = 5.0 Hz, 1 H, very slow exchange with D_2O), 11.24 (s, br, 1 H, rapid D_2O exchange); mass spectrum *m/e* 282 (M^+), 177 (M^+ − PhCO), 147 (PhCONCO), 121 ($PhCONH_2$), 105 (PhCO).

Anal. Calcd for $C_{16}H_{14}N_2O_3$: C, 68.08; H, 5.00; N, 9.92. Found: C, 68.43; H, 5.13; N, 10.09.

Reaction of 2,3-diphenyl-1-azirine (4a) with benzoyl isocyanate (1) was carried out as described above using 0.588 g (4 mmol) of 1 and 0.772 g (4 mmol) of **4a.** The adduct **9a** crystallized from ether–pentane as white needles (0.082 g, 6%): mp 133–134°; ir ν_{max} (Nujol) 1730 (C=O), 1565 (C=N) cm^{-1}; ^1H nmr δ_{TMS} ($CDCl_3$) 4.23 (s, 1 H), 7.05–8.24 (m, 15 H); mass spectrum *m/e* 193 (azirine), 147 (PhCONCO), 105 (PhCO), 103 (PhCN).

Anal. Calcd for $C_{22}H_{16}N_2O_2$: C, 77.63; H, 4.71; N, 8.23. Found: C, 77.50; H, 4.64; N, 8.11.

Hydrolysis of the Cycloadduct 9b. A suspension of **9b** in 10 ml of 1 *M* HCl was stirred at 25° for 18 hr. The white precipitate that resulted was filtered off, washed with water, and recrystallized from ethanol to give white needles (0.183 g, 86%): mp 137–138°; ir ν_{max} (Nujol) 3270, 3140 (NH), 1710 (C=O), 1680 (C=O), 1550 (amide II); ^1H nmr δ_{TMS} ($CDCl_3$) 1.53 (d, J = 6.9 Hz, 3 H), 5.54 (m, J = 6.9 Hz, 7.0 Hz, 1 H), 7.16–8.20 (m, 10 H), 9.63 (d, br, J = 7.0 Hz, 1 H, very slow exchange with D_2O), 10.08 (s, br, 1 H, rapid exchange with D_2O); mass spectrum *m/e* 296 (M^+), 191 (M^+ − PhCO), 147 (PhCONCO), 121 ($PhCONH_2$), 105 (PhCO).

Anal. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.90; H, 5.44; N, 9.45. Found: C, 68.57; H, 5.41; N, 9.48.

Thermolysis of Cycloadduct 9b. A solution of 0.278 g (1 mmol) of **9b** in 10 ml of toluene was heated under reflux for 2 hr and then separated on a silica gel column. Azirine (**4b**) (0.115 g) was eluted with 50% ether–pentane and benzamide (0.105 g) was eluted with 10% methanol–dichloromethane.

Kinetic measurements for the thermal decomposition of **9b** were done with a 0.572 *M* solution in *dry* $CDCl_3$ at 70° in a sealed (under N_2) nmr tube. The decomposition rate was followed by ^1H nmr. Careful and repeated integrations were done on the methyl groups of **9b** and **4b** (δ 1.17 and 1.36) and an internal cross-check with the aziridine proton of **9b** and the C-3 proton of **4b** (δ 3.19 and 2.28) was also done. These results are shown in Table I.

Reaction of 2,3-Diphenyl-1-azirine (4a) with Benzoyl Isothiocyanate (3). To a solution of 0.489 g (3 mmol) of benzoyl isothiocyanate (**3**) in 10 ml of benzene was added 0.386 g (2 mmol) of 2,3-diphenyl-1-azirine (**4a**) in 5 ml of benzene and the reaction mixture was heated under reflux for 12 hr. The solvent was removed and the residue was chromatographed on preparative plates carrying silica gel PF_{254} with 50% ether–pentane as the developing solvent. The cycloadduct (**12a**) crystallized from ether–pentane as white needles (0.483 g, 67.5%): mp 143–144°; ir ν_{max} (Nujol) 3270 (NH), 1675 (C=O), 1550 (amide II) cm^{-1}; ^1H nmr δ_{TMS} ($CDCl_3$) 6.85–7.95 (m, 15 H), 11.15 (s, br, 1 H, rapid exchange with D_2O); ^{13}C nmr δ_{TMS} ($CDCl_3$) 127.25, 127.57, 128.22, 128.76, 129.51, 131.83, 132.05, 132.54, 134.37, 144.51, 157.46, 165.33; mass spectrum *m/e* 356 (M^+), 328, 210, 192, 178, 165, 121, 105.

Anal. Calcd for $C_{22}H_{16}N_2OS$: C, 74.13; H, 4.52; N, 7.86. Found: C, 74.15; H, 4.64; N, 8.03.

Reaction of 3-Methyl-2-phenyl-1-azirine (4b) with Benzoyl Isothiocyanate (3). The cycloaddition was carried out as described above to give **12b** in 65% conversion as white needles: mp 138–139.5°; ir ν_{max} (Nujol) 3170 (NH), 1680 (C=O), 1545 (amide II) cm^{-1}; ^1H nmr δ_{TMS} ($CDCl_3$) 1.97 (s, 3 H), 7.24–8.10 (m, 10 H), 12.01 (s, br, 1 H, rapid exchange with D_2O); ^{13}C nmr δ_{TMS} ($CDCl_3$) 15.27, 126.28, 127.52, 128.17, 128.81, 129.03, 132.27, 132.80, 141.87, 157.62, 165.98; mass spectrum *m/e* 294 (M^+), 266, 191, 148, 121, 116.

Anal. Calcd for $C_{17}H_{14}N_2OS$: C, 69.36; H, 4.79; N, 9.52. Found: C, 69.35; H, 5.08; N, 9.34.

Reaction of 2-phenyl-1-azirine (4c) with benzoyl isothiocyanate (3) was carried out as described above but for 48 hr at 25°. The adduct **12c** was obtained in 15% yield as pale yellow needles: mp 212–213°; ir ν_{max} (Nujol) 3165 (NH), 1685 (C=O), 1570 (amide II) cm^{-1}; ^1H nmr δ_{TMS} ($CDCl_3$) 7.08 (s, 1 H), 7.21–8.15 (m, 10 H), 12.75 (s, br, 1 H, rapid exchange with D_2O); ^{13}C nmr δ_{TMS} ($CDCl_3$) 126.12, 127.90, 128.33, 128.87, 129.14, 136.67, 132.80, 133.02, 143.60, 159.51, 166.03; mass spectrum *m/e* 280 (M^+), 252, 134, 121, 105.

Anal. Calcd for $C_{16}H_{12}N_2OS$: C, 68.55; H, 4.32; N, 9.99. Found: C, 68.64; H, 4.63; N, 9.78.

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References and Notes

(1) V. Nair, *J. Org. Chem.*, **37,** 802, 2508 (1972).
(2) V. Nair, *Tetrahedron Lett.*, 4831 (1971).
(3) A. Hassner, A. S. Miller, and M. J. Haddadin, *Tetrahedron Lett.*, 1353 (1972).
(4) A. Hassner and D. J. Anderson, *J. Amer. Chem. Soc.*, **94,** 8255 (1972).
(5) J. Goerdeler and H. Schenk, *Chem. Ber.*, **98,** 2954 (1965).
(6) O. Tsuge and K. Sakai, *Bull. Chem. Soc. Jap.*, **45,** 1534 (1972.
(7) O. Tsuge and S. Kanemasa, *Bull. Chem. Soc. Jap.*, **45,** 2877, 3591 (1972).
(8) O. Tsuge and S. Kanemasa, *Tetrahedron,* **28,** 4737 (1972).
(9) A. G. Hortmann, D. A. Robertson, and B. K. Gillard, *J. Org. Chem.*, **37,** 322 (1972).
(10) A. Hassner and F. W. Fowler, *J. Amer. Chem. Soc.*, **90,** 2869 (1968).
(11) V. Nair and K. H. Kim, *Tetrahedron Lett.*, 1487 (1974).
(12) R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8,** 781 (1969).
(13) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Wiley, New York, N.Y., 1960, p 207.
(14) Exchange of the hydrogen bonded N–H in D_2O is rapid, as expected, when a drop of triethylamine is added.
(15) The lower yields in this case appear to be partly due to the formation of benzamide as a side product of the reaction.
(16) A. H. Cook, J. D. Downer, and I. Heilbron, *J. Chem. Soc.*, 1262 (1948).
(17) H. Ulrich, "Cycloaddition Reactions of Heterocumulenes," Academic Press, New York, N.Y. 1967.
(18) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967, p 634.
(19) K. Takatori and M. Ueda, *Pharm. Soc. Jap.*, **71,** 1373 (1951).
(20) H. A. Szymanski and R. E. Yelin, "NMR Band Handbook," Plenum Press, New York, N.Y., 1968, p 386.
(21) "Sadtler Standard Spectra," Sadtler, Philadelphia, Pa., 1962, 3636.
(22) R. R. Birge and P. A. Leermakers, *J. Amer. Chem. Soc.*, **94,** 8099 (1972).
(23) *Cf.* D. C. England and C. G. Krespan, *J. Org. Chem.*, **35,** 3312 (1970).
(24) V. Nair, *J. Org. Chem.*, **33,** 2121 (1968).
(25) J. Goerdeler and H. Horstmann, *Chem. Ber.*, **93,** 671 (1960).
(26) A. J. Speziale and L. R. Smith, *J. Org. Chem.*, **27,** 4361 (1962).
(27) L. F. Johnson and W. C. Jankowski, "Carbon-13 NMR Spectra," Wiley, New York, N.Y., 1972.

Di(2-*tert*-butylphenyl) Phosphorochloridate. A New Selective Phosphorylating Agent[1]

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A procedure for the preparation of 5′-nucleotides is described. 5′-Phosphates of adenosine, cytidine, uridine, guanosine, and thymidine were prepared directly from unprotected nucleosides in good yields by two-step synthesis using a new selective phosphorylating agent, di(2-*tert*-butylphenyl) phosphorochloridate (**1d**). The agent is stable, versatile, and highly selective for a primary hydroxyl in the presence of unprotected secondary hydroxy groups. The *tert*-butylphenyl protective groups are quite resistant toward dilute base and acid hydrolysis and are easily removed by hydrogenolysis in a nearly quantitative yield.

The polyfunctional nature and unique properties of nucleosides and carbohydrates present a considerable problem as to the choice of protective groups to achieve selectivity in phosphorylations. Recently, attention has been focused on the preparation of 5′-phosphates of various natural and synthetic compounds using selective phosphorylating agents.[2] A new phosphorylating agent has been explored, possessing the following properties: (a) ease of preparation, (b) relatively stable, (c) selective for the primary hydroxyl in the presence of unprotected secondary hydroxyls, (d) protective groups are stable under dilute base or acid conditions, and (e) protective groups are easily removable by hydrogenolysis.

This reagent does not offer any advantage over the phosphoryl chloride–triethyl phosphate procedure for the direct synthesis of 5′-mononucleotides.[2b] However, the presence of an acid and base stable protected 5′-phosphate group allows for further chemical modification of a nucleotide derivative prior to removal of the protective groups by hydrogenolysis.

Results and Discussion

Considering properties of phosphorylating agents studied previously,[2] and the spatial arrangement of various furanosides and pyranosides, it is reasonable to assume that steric hindrance can facilitate selective phosphorylation of the nucleoside primary hydroxy group in the presence of unprotected secondary hydroxy groups. In an effort to investigate this premise we synthesized phenolic esters of phosphate (**1a–f**) as potentially selective phosphorylating agents.

Phosphorochloridates **1a**, **1b**, **1c**, and **1d** were synthe-