Addition of Dimethyl Acetylenedicarboxylate to Imino Ethers. Trapping of a 1,4-Dipolar Intermediate

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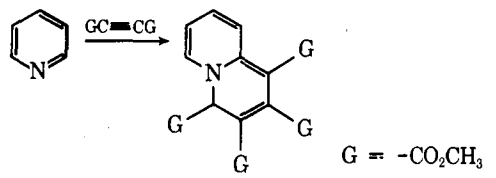
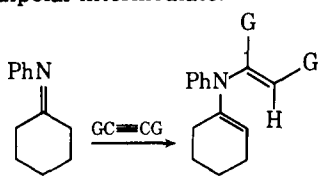
Received October 7, 1974

The *O*-alkylformimidates **1a** and **1b** react with dimethyl acetylenedicarboxylate (DMAD) to form 2:1 cycloadducts **2a** and **2b**. The 2-alkoxyazetines **6** (and **12**) react with DMAD to form 1:1 linear fumarate **7** (**13**) and maleate **8** (**14**) adducts via 1,4-dipolar ions like **9**. These 1,4-dipolar ions can also dimerize in nonpolar solvents to give the eight-membered ring 2:2 adducts **16** and **17**. The 1,4-dipolar ions postulated as intermediates in these reactions can be trapped with added water to give products **18**, **24–28**, and **31**.

The addition of electron-deficient acetylenes to carbon–nitrogen double bonds was first studied by Diels and Alder.[1] They found that aromatic heterocycles such as pyridine add dimethyl acetylenedicarboxylate (DMAD) to give a 2:1 adduct.[1–5] This reaction was later recognized by Huisgen to be one of a large class of reactions which are thought to proceed via 1,4-dipolar intermediates.[2–5] Analogous adducts have been found to incorporate two molecules of imine to one of DMAD; and 1:1:1 adducts of imine, DMAD, and phenyl isocyanate have been observed.[4,6]

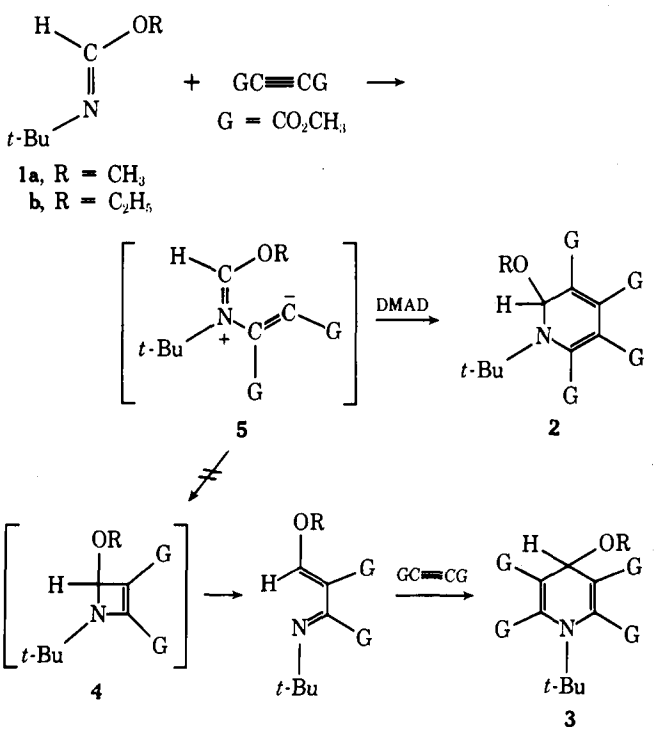


We report here the addition reactions of DMAD with a variety of imino ethers. Imino ethers are readily available by alkylation of amides and lactams[7] and might prove to be useful intermediates in heterocycle synthesis involving 1,4-dipolar additions. Of particular interest are the strained 1-azetines[7–11] derived from alkylation of β-lactams,[7,8] since they might give 1:1 adducts in the 1-azabicyclo[2.2.0]hexane system. Of the additions to imines studied,[12–20] only in the cases of additions of ynamines and enamines to C=N bonds have such cyclic 1:1 adducts been found,[16–20] although the 2-azetines formed in some cases ring open at low temperatures.[18,19] In a case of DMAD addition to an imine, a 1:1 type adduct was obtained, presumably via a 1,4-dipolar intermediate.[4–6]



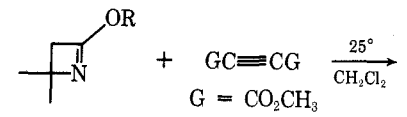
Results and Discussion

Additions of dimethyl acetylenedicarboxylate (DMAD) to the *N*-*tert*-butyl formimidates **1a** and **1b** give no 1:1 adducts, but 2:1 adducts **2a** and **2b** are formed in fair yields in boiling dioxane. The structures of the 2:1 adducts **2** are apparent from their spectral data. The asymmetric center to which the ethoxy group is attached in **2b** gives rise to an ABX_3 pattern for the diastereotopic methylene hydrogens of the ethoxy group instead of a simple quartet.[21] This rules out the structure **3** derived from ring opening of the 2-azetine **4**[13–15,22–26] followed by Diels–Alder reaction with DMAD.[25] The formation of **2** is most conveniently accounted for by capture of a 1,4-dipolar intermediate **5** by DMAD. The adducts **2a** and **2b** were the only products isolated regardless of the molar ratio of reagents.

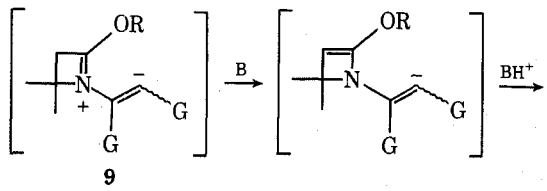


In contrast to the additions to **1**, the azetines **6a** and **6b** give primarily 1:1 adducts on addition of DMAD in dichloromethane solution. The reaction occurs readily under much milder conditions to give approximately a 50:50 mixture of the fumarate and maleate esters **7** and **8** in greater than 50% yield. The structures of **7** and **8** are apparent from their NMR spectra; the two different vinyl singlets and two different vinyl heptets (A part of an AX_3Y_3) are well accommodated by this assignment. These products are formed in dichloromethane independent of the molar ratio or order of addition of the reagents. No evidence was found for formation of the 1:1 adduct **11** or the 2:1 adduct analogous to **2**. Apparently **7** and **8** are formed by proton abstraction from the 1,4-dipole **9** and ring opening of 2-azetine **10**. The formation of **10** is analogous to the known ene-type reactions of DMAD and imines with abstractable hydrogens.[4–6] The geometry of **9** and the formation of both products **7** and **8** eliminate the possibility of an intramolecular proton abstraction. 2-Azetines are known to ring open readily.[13–15,22–24,26] Analogously to **6**, the azetine **12** gives esters **13** and **14** in 26% yield. The low yield can be attributed to steric hindrance by the 3-methyl substituent in the proton abstraction. A tertiary amine base was added to facilitate proton removal.

Since there are no abstractable hydrogens in the tetramethylazetines **15a** or **15b**, they cannot give 1:1 adducts analogous to **7** and **8**. Instead, on reaction with DMAD at



6a, R = CH_3
b, R = C_2H_5



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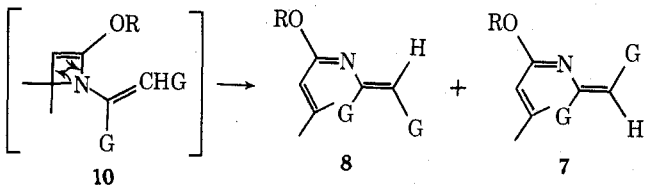
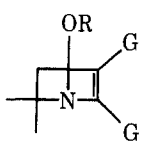


10 **8** **7**



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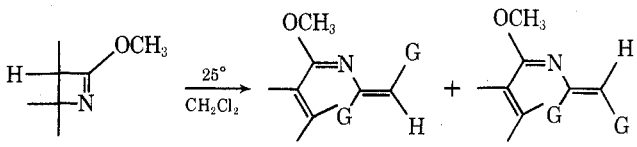
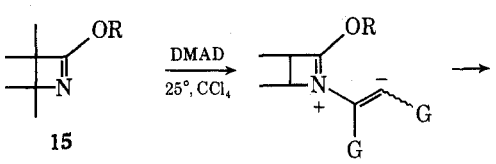


12 **13** **14**

+
GC≡CG

25° in methylene chloride, they give only polymers and recovered azetine. In carbon tetrachloride solvent, however, a new high molecular weight product **16b** (from **15b**) is



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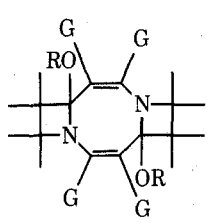
a, R = CH_3
b, R = C_2H_5



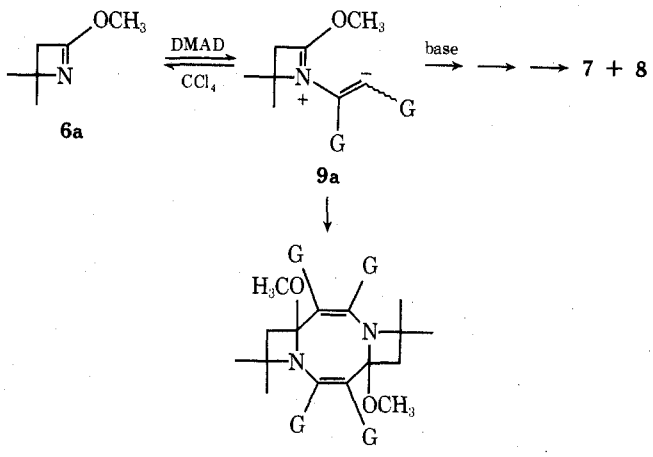
16

formed in 88% yield after distillation. This product and the related methoxy derivative **16a** have NMR spectra consistent with a 1:1 ratio of reactants but the boiling points and mass spectra are those expected for a 2:2 adduct. From the symmetry of the NMR spectra, the eight-membered ring structure **16a,b** is indicated, but a distinction between syn and anti fusions of the azetidine rings is not possible. They have a twofold axis and center of inversion, respectively, and should show the same symmetry in their NMR spectra. The asymmetry of the centers of ethoxyl group attachment is indicated by a complicated pattern for the diastereotopic methylene hydrogens of the ethoxyl in **16b**. This product appears to be formed simply by dimerization of a 1,4-dipolar intermediate. There is little precedent for these sorts of dimers in 1,4-dipolar ion chemistry.[27]

Table I
Ratios of 1:1 and 2:2 Products from 6a

[6a], *M*	[DMAD], *M*	Solvent	Ratio of [7] + [8]:[17]
0.82	1.16	CCl_4	0.7
0.41	0.58	CCl_4	0.7
0.13	0.13	CCl_4	1.3
0.34	0.48	1.6 *M* *N*-methylpiperidine in CCl_4	4
0.082	0.116	CH_2Cl_2	>10

Although no 2:2 dimer could be detected from **6a** in dichloromethane solvent, the dimer **17** was found to form in 35% yield along with 35% of a 1:1 mixture of **7** and **8** in carbon tetrachloride solution. Again the boiling point and mass spectrum indicated a 2:2 adduct, while the NMR spectrum has the symmetry expected of an eight-membered ring dimer **17**.

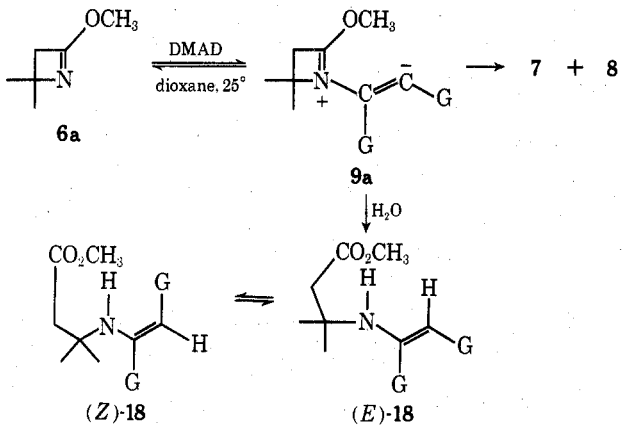


6a **9a** **17**

The variation in the ratio of 1:1 products **7** and **8** to the 2:2 product **17** with different reaction conditions is shown in Table I. The most dramatic effect is the lack of any observable 2:2 adduct in dichloromethane solvent. This can be explained as a consequence of the competition between the charge destroying dimerization step, **9a** → **17**, and a more polar transition state for proton abstraction by base in forming **7** and **8**. The 2:2 adducts **16a,b** are also strongly favored in nonpolar solvent. Interestingly, the rate of reaction of **6a** in dichloromethane is essentially identical with that in carbon tetrachloride, suggesting that the rate-determining step in these reactions is not simply the formation of the 1,4-dipolar ion, since such a reaction should be strongly accelerated in polar solvents.[28]

Normally the imino ether **6a** must act as the base in the hydrogen abstraction step, but in the presence of 1.6 *M* *N*-methylpiperidine the rate of formation of **7** and **8** increases relative to the rate of dimerization of **9a** in accord with the postulated mechanism. Increased reagent concentrations favor the 2:2 adduct over the 1:1 adduct as expected from a mechanism overall fourth order for **17** and third order for **7** and **8** (using **6a** as the base). This effect may not appear as large as expected because of the competing solvent polarity effect at high reagent concentrations. The rates of these reactions were followed approximately by NMR and showed the expected increases at high reagent concentrations. The data in Table I thus appear consistent with a mechanism involving a common 1,4-dipolar intermediate for the products **7**, **8**, and **17**.

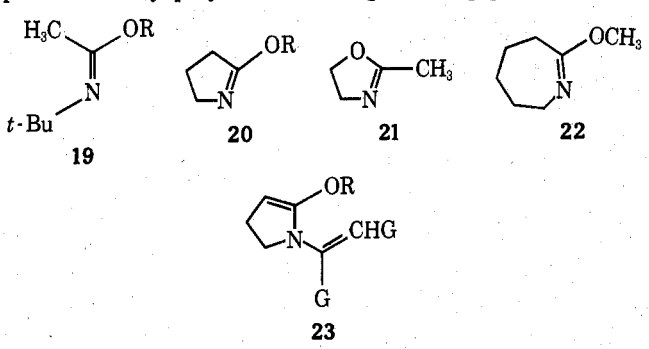
To confirm the presence of a 1,4-dipolar ion **9a** in these reactions, the addition of DMAD to **6a** was carried out in dioxane at 25° in the presence of water. A mixture was iso-



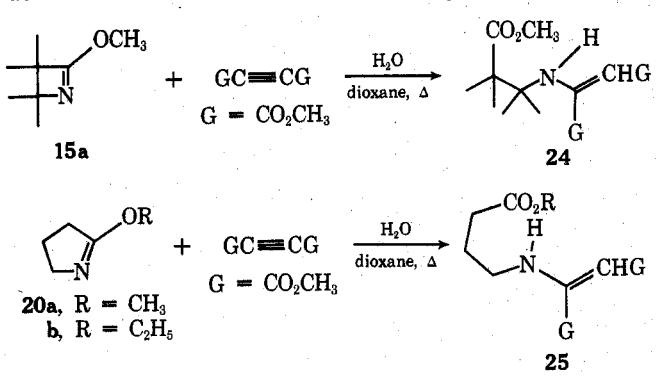
lated containing 75% of a trapping product 18 along with 17% of 7 and 8% of 8 by NMR analysis. Product 18 is initially formed as a 2:1 mixture of isomers (*E*)-18, with maleate configuration, and (*Z*)-18, with the fumarate configuration. On work-up and distillation the maleate isomer isomerizes to favor (*Z*)-18 by 10:1. These configurational assignments were made on the basis of the usual preference in amine additions to DMAD[29] for the fumarate isomer at equilibrium. The chemical shifts of the vinyl hydrogens at δ 4.78 for (*E*)-18 and δ 4.81 for (*Z*)-18 are ambiguous,[29,30] however, and the configurational assignments are only tentative.

Under identical conditions, but with no DMAD present, no hydrolysis of **6b** occurs. This eliminates the possibility that 18 might have been formed by reaction of an amino ester from hydrolysis of **6a** with DMAD,[31,32] and further implicates the 1,4-dipole **9a** as an intermediate in these reactions.

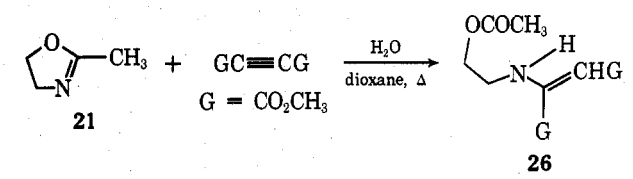
Attempted additions of DMAD to the imino ethers **19–22** produced only polymeric and high boiling products, per-



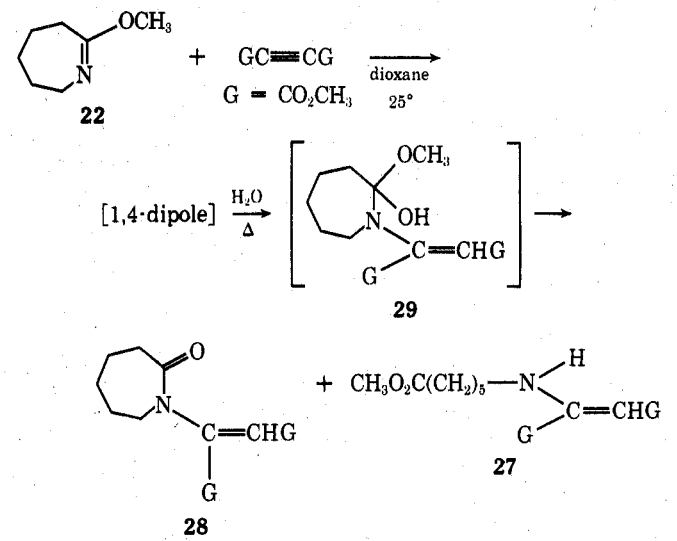
haps via hydrogen abstraction reactions to enamines like **23** followed by further condensation reactions with DMAD. In the reactions of imino ethers **15a** and **20a,b** with DMAD in boiling aqueous dioxane, however, the water trapping products **24** and **25** are isolated in moderate yields. In the reac-



tion of imino ether **21** and DMAD in the presence of water, approximately 40% of product **26** is isolated. These struc-

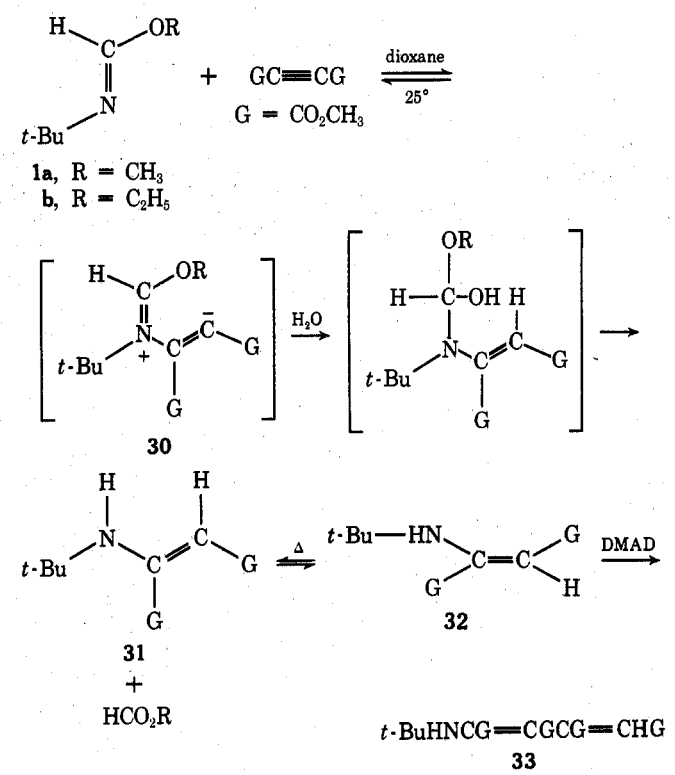


tures follow from spectral data and comparison of analogous products (**18, 24, 25**).[33] When water is added to the reaction mixture of **22** and DMAD at 100°, a mixture of products is obtained. The mixture is composed of ca. 50% of the ester enamine **27** and ca. 50% of the caprolactam **28** as analyzed by NMR. It is curious that only imino ether **22** gave an amide product **28**. This product **28** could not have come from the addition of caprolactam and DMAD, because amides and lactams add only under drastic conditions.[34] The amide **28** could come from the initial water



trapping product **29** of the 1,4-dipole. Cyclization of **27** to **28** was shown not to occur under the reaction conditions.

With the acyclic imino ethers **1a** and **1b**, heating to 100° with dioxane, DMAD, and water gives 59% of product **31**.



With excess DMAD under identical conditions, 29% of product **33** is isolated. Performing the reaction at room temperature, 46% of product **31** is isolated. Under the same conditions, but without added DMAD, no hydrolysis of imino ether **1b** occurs. Product **31** must come from water trapping of the 1,4-dipole **30** derived from imino ether **1** and DMAD at room temperature (analogous to azetine **6**). With excess DMAD, product **32** probably cycloadds to DMAD and ring expands to give product **33** (analogous to reactions of other enamines with DMAD).[24]

The imino ethers **1b** and **6b** were shown not to hydrolyze at 25° in dioxane–water,[35] confirming that these water trapping experiments involve interception of a 1,4-dipolar intermediate rather than hydrolysis followed by DMAD addition.[29] Reactions of iminosulfuranes with DMAD in the presence of water have been postulated to involve trapping of a 1,4-dipolar intermediate,[22] but no control experiments were run to test the possibility of hydrolysis of the iminosulfuranes.[36]

The rate of disappearance of **1b** increases tenfold on addition of water to the reaction mixture in dioxane at 25°. This suggests that the rate-limiting step in the 1,4-dipolar reaction of **1b** to give **2** is not the addition of DMAD to **1b** to give **30**, but the addition of **30** to DMAD.

Experimental Section

All boiling points and melting points are uncorrected. Ir spectra were obtained neat or in solution with a matched reference cell on a Perkin-Elmer 337 grating infrared spectrophotometer. Uv spectra were recorded on a Cary 15 Spectrophotometer. NMR spectra were obtained on a 60-MHz Varian Associates T-60 or a Jeolco C-60H spectrometer. Where indicated, 100-MHz spectra were obtained on a Varian HA-100 spectrometer. Mass spectra were obtained on a MS-902 spectrometer or on a Finnigan 1015 quadrupole spectrometer where indicated.

Materials. The dimethyl acetylenedicarboxylate (DMAD) was purchased from Aldrich Chemical Co. and freshly distilled before use. The imino ethers were either purchased from Aldrich Chemical Co. or made by alkylation of the corresponding amide with a trialkyloxonium fluoroborate.[37]

***O*-Ethyl *N*-*tert*-butylformimidate (1b)** was prepared by standard procedures[37] from *N*-*tert*-butylformamide and triethyloxonium fluoroborate in 73% yield: bp 118–122°; ir (neat) 2950, 1650, 1380 cm^{-1}; NMR (CCl_4) δ 1.10 (s, 9 H), 1.18 (t, J = 7.1 Hz, 3 H), 3.94 (q, J = 7.1 Hz, 2 H), 7.23 (s, 1 H); mass spectrum (70 eV) *m/e* 129.1156 (calcd for $C_7H_{15}NO$, 129.1154); *m/e* (rel intensity) 129 (M^+, 28), 114 (100), 101 (17), 87 (2), 86 (56), 85 (9), 84 (2), 73 (5), 72 (4), 71 (3), 69 (3), 59 (3), 58 (95), 57 (95), 56 (22), 55 (7), 46 (46), 45 (19), 44 (5), 43 (7), 42 (29), 41 (53), 40 (4), 39 (17).

Reaction of DMAD with 1a. A solution composed of 316 mg (2.75 mmol) of **1a** and 780 mg (5.50 mmol) of DMAD in 20 ml of 1,2-dichloroethane was refluxed for 24 hr. The solvent was removed in vacuo leaving a viscous residue. Upon addition of ether to the residue, a white solid precipitated out of solution. Recrystallization from methanol gave 548 mg (50%) of **2a:** mp 144.5–146.5°; ir ($CHCl_3$) 2950, 1750, 1725, 1600 cm^{-1}; uv (ethanol) 215 nm (ϵ 13,500), 278 (14,000), 345 (10,200); NMR (CCl_4) δ 1.50 (s, 9 H), 3.58 (s, 3 H), 3.67 (s, 6 H), 3.92 (s, 3 H), 5.43 (s, 1 H); mass spectrum (70 eV) *m/e* 399.1526 (calcd for $C_{18}H_{25}NO_9$, 399.1529); *m/e* (rel intensity) 399 (M^+, 3), 369 (1), 368 (3), 354 (1), 241 (3, 240 (16, 313 (3, 298 (3), 286 (2), 285 (9), 284 (77), 266 (4), 253 (2), 252 (12), 251 (100), 237 (5), 224 (1), 205 (2), 194 (1), 178 (2), 167 (1), 166 (1), 151 (1), 137 (1), 135 (2), 79 (1), 77 (1), 59 (5), 58 (1), 57 (30), 56 (2), 55 (2), 45 (2), 44 (2), 42 (3), 41 (11), 39 (2).

Reaction of DMAD with 1b. Following the procedure for **1a** above, 392 mg (3.04 mmol) of **1b** and 470 mg (3.30 mmol) of DMAD in 10 ml of dichloromethane resulted in 460 mg (67%) of **2b:** mp 155.5–156.5°; ir ($CHCl_3$) 2950, 1740, 1680, 1595 cm^{-1}; NMR (100 MHz) ($CDCl_3$) δ 1.46 (t, $J_{AX} = J_{BX} = 7.0$ Hz, 3 H) (X part of ABX_3), 1.54 (s, 9 H), 3.66 (s, 6 H), 3.71 (s, 3 H), 3.86 (s, 3 H), 4.07 (dq, $J_{BX} = 7.0$, $J_{AB} = 9.5$ Hz, 1 H) (B part of ABX_3), 4.53 (dq, $J_{AX} = 7.0$, $J_{AB} = 9.5$ Hz, 1 H) (A part of ABX_3, AB spectrum obtained from time averaged computer technique), 5.66 (s, 1 H); mass spectrum (70 eV) *m/e* 413.1689 (calcd for $C_{19}H_{27}NO_9$, 413.1686); *m/e* (rel intensity) 413 (M^+, 10), 382 (12), 355 (8), 354 (47), 326 (12), 299 (17), 298 (100), 267 (32), 266 (100), 238 (83), 206 (33), 178 (25), 59 (25), 57 (83), 41 (42).

Reaction of DMAD with 6a. A mixture of 279 mg (2.46 mmol) of **6a** and 348 mg (2.45 mmol) of DMAD in 10 ml of dichloromethane was left at room temperature for 24 hr. Evaporation of solvent in vacuo left an oil residue. The residue was chromatographed on alumina using carbon tetrachloride and vacuum distilled, yielding 338 mg (54%), bp 100–110° (0.1 mm), of a mixture composed of approximately equal amounts of fumarate (**7a**) and maleate (**8a**) isomers. The fumarate isomer **7a** could be enriched in early short-path distillation fractions. The spectral data are listed: ir (CCl_4) 2950, 1740 (sh), 1725, 1670, 1630, 1440 cm^{-1}; NMR (100 MHz, CCl_4) for **7a** δ 1.79 (d, J = 1.4 Hz, 3 H), 1.90 (d, J = 1.4 Hz, 3 H), 3.60 (s, 3 H), 3.74 (s, 6 H), 5.35 (heptet, J = 1.4 Hz, 1 H), 6.01 (s, 1 H) (assigned fumarate isomer);[38] for **8a,** δ 1.92 (d, J = 1.4 Hz, 3 H), 1.98 (d, J = 1.4 Hz, 3 H), 3.64 (s, 3 H), 3.76 (s, 3 H), 3.82 (s, 3 H), 5.08 (s, 1 H), 5.78 (heptet, J = 1.4 Hz, 1 H) (assigned maleate isomer);[38] mass spectrum (70 eV) *m/e* 255.1113 (calcd for $C_{12}H_{17}NO_5$, 255.1107); *m/e* (rel intensity) 255 (M^+, 2), 224 (2), 196 (80), 164 (100), 136 (30), 115 (20), 114 (20), 113 (30), 85 (20), 83 (50), 82 (20), 59 (40), 55 (40), 53 (20), 41 (20), 39 (30).

Reaction of DMAD with 6b. Following the procedure for **6a,** 73 mg (0.58 mmol) of **6b** and 92 mg (0.65 mmol) of DMAD yielded 78 mg (50%) of a 1:1 mixture of fumarate (**7b**) and maleate (**8b**) isomers: bp 114° (0.2 mm); ir (neat) 2950, 1740 (sh), 1730, 1670, 1630, 1440 cm^{-1}; uv (ethanol) 220 nm (ϵ 15,000), 226 (11,000); NMR (CCl_4) for **7b** δ 1.39 (t, J = 9.7 Hz, 3 H), 1.75 (d, J = 1.3 Hz, 3 H), 1.80 (d, J = 1.3 Hz, 3 H), 3.57 (s, 3 H), 3.71 (s, 3 H), 4.14 (q, J = 9.7 Hz, 2 H), 5.26 (m, $J \simeq$ 1.3 Hz, 1 H), 5.92 (s, 1 H) (assigned fumarate isomer);[38] for **8b** δ 1.33 (t, J = 9.7 Hz, 3 H), 1.88 (d, J = 1.3 Hz, 3 H), 1.95 (d, J = 1.3 Hz, 3 H), 3.61 (s, 3 H), 3.71 (s, 3 H), 4.24 (q, J = 9.7 Hz, 2 H), 4.99 (s, 1 H), 5.69 m, $J \simeq$ 1.3 Hz, 1 H) (assigned maleate isomer);[38] mass spectrum (Finnigan) (70 eV) *m/e* (rel intensity) 270 (1.3), 269 (M^+, 1.3), 254 (0.5), 238 (8), 237 (1.7), 224 (1.5), 211 (8), 210 (57), 178 (94), 150 (60), 128 (25), 122 (33), 101 (15), 100 (17), 97 (20), 96 (17), 94 (19), 84 (24), 83 (100), 82 (100), 69 (22), 68 (31), 67 (23), 59 (18), 55 (80), 54 (33), 53 (67), 43 (17), 42 (17), 41 (35), 39 (81).

Reaction of DMAD with 12. Following the procedure for **6a** with the addition of 1 drop of ethyldiisopropylamine, 105 mg (0.83 mmol) of **12** and 120 mg (0.84 mmol) of DMAD yielded 58 mg (26%) of a 1:1 mixture of fumarate (**13**) and maleate (**14**) isomers: bp 100–110° (10^{-3} mm); ir (CCl_4) 2970, 1740 (sh), 1725, 1640, 1620, 1440 cm^{-1}; NMR (CCl_4) for **13** δ 1.60 (s, 6 H), 1.68 (s, 3 H), 3.58 (s, 3 H), 3.68 (s, 6 H), 5.90 (s, 1 H) (assigned as fumarate isomer);[38] for **14** δ 1.60 (s, 6 H), 1.68 (s, 3H), 3.60 (s, 3 H), 3.74 (s, 3 H), 3.80 (s, 3 H), 5.13 (s, 1 H) (assigned as maleate isomer);[38] mass spectrum (70 eV) *m/e* 269.1256 (calcd for $C_{13}H_{19}NO_5$, 269.1263); *m/e* (rel intensity) 269 (M^+, 10), 254 (3), 239 (12), 222 (3), 210 (67), 194 (5), 183 (7), 179 (10), 178 (100), 151 (12), 150 (20), 97 (5), 96 (7), 95 (8), 69 (12), 68 (13), 67 (13), 59 (8), 55 (10), 53 (18), 44 (12), 43 (5), 42 (8), 41 (47), 40 (3), 39 (13).

Reaction of 6a with DMAD in Carbon Tetrachloride. A mixture of 147 mg (1.30 mmol) of **6a** and 184 mg (1.29 mmol) of DMAD in 10 ml of carbon tetrachloride was left at 25° for 24 hr. A mixture composed of 35% yield each of the 1:1 isomers **7** and **8** and 2:2 adduct was found by NMR. Vacuum distillation afforded two fractions: 184 mg (53%), bp <140° (10^{-3} mm), containing mostly isomers **7a** and **8a,** and 143 mg (47%), bp 140–180° (10^{-3} mm). The higher boiling fraction was chromatographed on alumina with dichloromethane elution and redistilled, giving **17:** bp 150° (10^{-3} mm); ir (CCl_4) 2950, 1745, 1730 (sh), 1555, 1435 cm^{-1}; NMR (CCl_4) δ 1.58 (s, 3 H), 1.73 (s, 3 H), 2.64 (s, 2 H), 3.47 (s, 3 H), 3.67 (s, 3 H), 3.72 (s, 3 H); mass spectrum (70 eV) *m/e* (rel intensity) no parent observable, 425 (0.4), 423 ($M^+ - C_4H_8 - OCH_3$,1), 421 (0.8), 411 (4), 409 (8), 407 (6), 380 (4), 378 (6), 376 (4), 304 (10), 292 (24), 290 (72), 258 (30), 235 (28), 233 (100), 174 (18), 166 (26), 160 (20), 73 (28), 59 (40), 55 (32), 41 (40),

Reaction of 15b with DMAD in Carbon Tetrachloride. Following the procedure for **6a** above with 1 ml of carbon tetrachloride, 144 mg (0.93 mmol) of **15b** and 134 mg (0.94 mmol) of DMAD gave a high-boiling oil. Chromatography on alumina with diethyl ether elution and redistillation gave 245 mg (88%) of high-boiling oil **16b:** bp 150–160° (0.07 mm); ir (CCl_4) 2950, 1750, 1735 (sh), 1570, 1440, 1270 cm^{-1}, nearly identical with that of **17;** NMR (CCl_4) δ 1.07 (t, J = 6.8 Hz, 3 H), 1.25 (s, 3 H), 1.37 (s, 3 H), 1.44 (S= 6 H), 3.48 (s, 3 H), 3.54 (s, 3 H), ca. 3.7 (m, 2 H). The mass spectrum (Finnigan) indicated peaks up to *m/e* 440 with a pattern similar to that of **17.** In dichloromethane solvent this reaction gave only recovered imino ether and polymer.

Reaction of 15a with DMAD in Carbon Tetrachloride. Following the procedure for **6a** above and using 1 ml of carbon tetrachloride, 271 mg (1.92 mmol) of **15a**, and 273 mg (1.92 mmol) of DMAD resulted in an exothermic reaction. Chromatography on alumina with dichloromethane elution and distillation gave a clear oil, **16a**: bp 140–160° (0.1 mm); ir (CCl_4) 2940, 1740, 1560 cm^{-1}, nearly identical with that of **17**; NMR (CCl_4) δ 1.22 (s), 1.36 (s), 1.40 (broad s), and 1.55 (s) (ca. 24 H), 3.62 (s), 3.70 (s), and 3.75 (s) (ca. 18 H); mass spectrum (Finnigan) *m/e* up to ca. 450 with a pattern similar to that of **16b**. In chloroform and dichloromethane solvent, this reaction gives only recovered imino ether and polymer.

Attempted Reaction of DMAD with Imino Ethers 19–22. Following the procedure of **1b**, equimolar amounts of the above imino ethers and DMAD resulted in the production of polymers, both with and without total consumption of the imino ether.

Reaction of DMAD with 6a in the Presence of Water. A solution of 334 mg (2.96 mmol) of **6a**, 422 mg (2.98 mmol) of DMAD, and 76 mg (4.22 mmol) of water in 10 ml of dioxane was left at 25° for 24 hr. The NMR spectrum of the crude reaction mixture showed 75% of product **18**, 17% of fumarate **7a**, and 8% of maleate **8a** on evaporation of the solvent. Chromatography on alumina with dichloromethane elution and vacuum distillation afforded 477 mg (59%) of product **18**: bp 110–120° (0.8 mm); ir (CCl_4) 3250, 2950, 1745, 1670, 1620, 1205 cm^{-1}; NMR (CCl_4) δ 1.42 (s, 6 H), 2.70 (s, 2 H), 3.65 (s, 6 H), 3.82 (s, 3 H), 4.81 (s, 1 H), 8.30 (s, 1 H, NH); mass spectrum (70 eV) *m/e* 273.1216 (calcd for $C_{12}H_{19}NO_6$, 273.1212); *m/e* (rel intensity) 273 (20), 245 (16), 242 (8), 214 (12), 200 (20), 196 (100), 185 (68), 172 (44), 164 (96), 160 (24), 159 (32), 140 (76), 136 (48), 128 (40), 115 (28), 112 (32), 100 (32), 87 (24), 83 (48), 82 (28), 73 (40), 68 (32), 59 (40), 55 (48), 43 (60). This sample was tentatively assigned the fumarate, (*Z*)-**18** configuration but contained a trace of (*E*)-**18** as indicated by a small peak at δ 4.78 in a 1:10 ratio to the peak at δ 4.81 for (*Z*)-**18**. The NMR spectrum of the crude reaction mixture showed a 2:1 ratio of isomers (*E*)-**18** to (*Z*)-**18**.

Reaction of DMAD with 15a in the Presence of Water. After a solution of 320 mg (2.27 mmol) of **15a**, 323 mg (2.27 mmol) of DMAD, and 43 mg (2.39 mmol) of water in 10 ml of dioxane was heated to 110° for 24 hr, 350 mg (51%) of **24** was isolated on distillation: bp 100° (3×10^{-3} mm); ir (CCl_4) 3350, 2940, 1740 cm^{-1}; NMR (CCl_4) δ 1.26 (s, 12 H), 3.60 (s, 3 H), 3.67 (s, 3 H), 3.77 (s, 3 H), 4.65 (s, 1 H), 8.50 (s, 1 H).

Reaction of DMAD with 20a in the Presence of Water. Following the preceding procedure for preparation of **24**, 5.31 mg (4.70 mmol) of **20a**, 673 mg (4.73 mmol) of DMAD, and 110 mg (6.10 mmol) of water gave 464 mg (38%) of product **25a**: bp 120–140° (0.1 mm); ir (CCl_4) 3300, 2950, 1745, 1670, 1620, 1445 cm^{-1}; NMR (CCl_4) δ 1.83 (m, 2 H), 2.32 (m, 2 H), 3.40 (m, 2 H), 3.68 (s, 6 H), 3.85 (s, 3 H), 5.00 (s, 1 H), 8.15 (br d, 1 H); mass spectrum (Finnigan) (50 eV) 260 (0.07), 259 (M^+, 0.2), 228 (0.6), 227 (0.6), 212 (0.3), 200 (0.5), 196 (4), 195 (5), 180 (1), 172 (6), 168 (2), 167 (2), 166 (1), 154 (9), 153 (3), 141 (6), 140 (31), 136 (2), 128 (4), 126 (7), 125 (3), 112 (26], 108 (23), 101 (43), 100 (7), 94 (5), 82 (16), 69 (23), 68 (23), 59 (100), 55 (18), 54 (10), 53 (13), 45 (28), 43 (10), 42 (15), 41 (43), 39 (10). The adduct **25a** was alternatively synthesized by treating the product from acidic methanolysis of 2-pyrrolidone with DMAD under basic conditions (added solid sodium bicarbonate).

Reaction of DMAD with 20b in the Presence of Water. Following the procedure for preparation of **24**, 228 mg (2.02 mmol) of **20b**, 287 mg (2.02 mmol) of DMAD, and 38 mg (2.10 mmol) of water gave 231 mg (42%) of **25b**: bp 130–150° (0.1 mm); ir (neat) 3300, 1750, 1670, 1620 cm^{-1}; NMR (HA-100) (CCl_4) δ 1.23 (t, J = 7.1 Hz, 3 H), 1.85 (m, 2 H), 2.25 (m, 2 H), 3.35 (m, 2 H), 3.64 (s, 3 H), 3.82 (s, 3 H), 4.07 (q, J = 7.1 Hz, 2 H), 5.00 (s, 1 H), 8.13 (s, 1 H, NH).

Reaction of DMAD with 21 in the Presence of Water. Following the preceding procedure for preparation of **24**, 292 mg (3.44 mmol) of **21**, 489 mg (3.44 mmol) of DMAD, and 76 mg (4.22 mmol) of water gave 315 mg (37%) of **26**; bp 114–124° (0.1 mm); ir (CCl_4) 3300, 2950, 1750, 1675, 1620, 1210 cm^{-1}; NMR (CCl_4) δ 2.02 (s, 3 H), 3.55 (t, $J \simeq 5$ Hz, 2 H), 3.60 (s, 3 H), 3.78 (s, 3 H), 4.10 (t, $J \simeq 5$ Hz, 2 H), 5.08 (s, 1 H), 8.12 (s, 1 H, NH); mass spectrum (70 eV) *m/e* 245.0908 (calcd for $C_{10}H_{15}NO_6$, 245.0899); *m/e* (rel intensity) 245 (M^+, 3.2) 214 (9), 185 (90), 172 (54), 153 (9), 140 (90), 126 (18), 125 (13), 112 (36), 94 (13), 87 (27), 68 (18), 59 (13), 45 (36), 44 (36), 43 (100), 42 (9).

Reaction of DMAD with 22 in the Presence of Water. Following the preceding procedure for preparation of **24**, 610 mg (4.80 mmol) of **22** and 683 mg (4.80 mmol) of DMAD with excess water gave a mixture composed of 70% **27** and 30% amide **28** by NMR analysis. Fractional distillation gave 477 mg (35%) of **27**: bp ~160° (0.15 mm); ir (CCl_4) 3450, 3280, 2950, 1745 (s), 1670, 1615, 1440 cm^{-1}; NMR (CCl_4) δ 1.50 (m, 6 H), 2.20 (m, 2 H), 3.35 (m, 2 H), 3.60 (s, 3 H), 3.80 (s, 3 H), 4.97 (s, 1 h), 8.10 (s, 1 H, NH); mass spectrum (70 eV) *m/e* 287.1356 (calcd for $C_{13}H_{21}NO_6$, 287.1369); *m/e* (rel intensity) 287 (M^+, 20), 272 (0.4), 256 (17), 255 (24), 228 (20), 224 (34), 223 (10), 197 (10), 196 (100), 184 (7), 173 (10), 172 (30), 168 (10), 167 (20), 164 (7), 154 (20), 141 (10), 140 (45), 129 (14), 128 (10), 126 (7), 114 (7), 113 (7), 112 (17), 100 (14), 97 (17), 87 (7), 82 (10], 69 (50), 68 (24), 67 (7), 59 (24), 55 (42), 54 (7), 53 (10), 45 (24), 44 (7), 43 (10), 42 (14), 41 (50), 39 (14). Subjecting the sample **27** to the experimental conditions (refluxing aqueous dioxane) for 8 hr results in decomposition of **27** with no formation of **28**.

Distillation of late fractions from chromatography on alumina with carbon tetrachloride elution gave 150 mg (15%) of amide **28**: bp 170° (0.3 mm); ir (CCl_4) 2950, 1740 (s), 1695, 1615, 1440, 1370 cm^{-1}; NMR (CCl_4) δ 3.62 (s, 3 H), 3.68 (s, 3 H), 5.52 (s, 1 H), and broad multiplets at 1.75 and 2.50; mass spectrum (70 eV) *m/e* (rel intensity) 255 (M^+, 4.5), 224 (3.5), 198 (3.5), 197 (16), 196 (100), 186 (3.5), 185 (16), 168 (4.5), 164 (8), 160 (3.5), 154 (7), 140 (3.5), 128 (6), 127 (6), 126 (35), 113 (3.5), 112 (7), 108 (6), 101 (4.5), 100 (7), 99 (3.5), 98 (28), 96 (6), 84 (6), 82 (3.5), 81 (4.5), 69 (7), 68 (6), 67 (6), 59 (6), 56 (6), 55 (14), 53 (4.5), 45 (4.5), 44 (6), 43 (3.5), 42 (19), 41 (29), 40 (4.5), 39 (8); mass spectrum (70 eV) *m/e* 255.1113 (calcd for $C_{12}H_{17}NO_5$, 255.1107).

The progress of a reaction mixture containing 127 mg of **22**, 142 mg of DMAD, and 730 μl of dioxane at 35° was followed by NMR. On addition of 70 μl of water, the rate of disappearance of **22** increased about tenfold and was complete within 3 hr. No **28** was formed under these conditions.

Formation of 31 from 1b and DMAD in the Presence of Water at 25°. A solution composed of 128 mg (0.85 mmol) of **1b**, 114 mg (0.80 mmol) of DMAD, and 14.5 mg (0.80 mmol) of water was left at room temperature for 11 hr. The NMR spectrum indicated complete consumption of imino ether **1b**. The sample was evaporated in vacuo and chromatographed on alumina with dichloromethane elution. Vacuum distillation gave 80 mg (46%) of product **31**: bp 90–100° (0.15 mm); ir (neat) 3330, 2940, 1745, 1665, 1600 cm^{-1}; NMR (CCl_4) δ 1.32 (s, 9 H), 3.57 (s, 3 H), 3.75 (s, 3 H), 4.65 (s, 1 H), 8.22 (br s, 1 H, NH) along with a minor (20%) isomer **32** δ 1.35 (s, 9 H), 3.54 (s, 3 H), 3.73 (s, 3 H), 4.69 (s, 1 H); mass spectrum (70 eV) *m/e* 215.1161 (calcd for $C_{10}H_{17}NO_4$, 215.1157); *m/e* (rel intensity) 215 (M^+, 42), 200 (33), 184 (16), 168 (25), 160 (25), 159 (83), 140 (25), 128 (100), 101 (42), 100 (83), 68 (66), 57 (100), 41 (92).

When the reaction was monitored by NMR at 35° on a mixture 0.82 *M* in **1b** and 1.16 *M* in DMAD in dioxane, the rate of disappearance of **1b** increased tenfold on addition of 10% water with complete disappearance occurring within 40 min.

The reaction of **1a** under identical conditions gave the same ratio of products with the same ir and NMR spectra. Products **31** and **32** were independently synthesized by treating DMAD with *tert*-butylamine in ether at room temperature[29a] and found to have identical ir and NMR spectra. The initial mixture at room temperature contained almost exclusively **31**, which was converted on heating at 80° in CCl_4 for 2 hr to a 10:1 mixture of **32** to **31** at equilibrium.

Formation of 31 from 1b and DMAD in the Presence of Water at 100°. A solution composed of 413 mg (3.20 mmol) of **1b** and 460 mg (3.24 mmol) of DMAD in 10 ml of 2% aqueous dioxane was refluxed for 24 hr. Vacuum distillation afforded 376 mg (59% yield) of a mixture of products **31** (80%) and **32** (20%), bp 70–80° (0.07 mm).

Following the procedure above, but with excess DMAD, 375 mg (2.90 mmol) of **1b** and 831 mg (5.85 mmol) of DMAD gave 254 mg (29%) of product **33**: bp 150–160° (0.3 mm); ir (neat and dilute CCl_4) 3220, 2940, 1745–1730, 1660, 1598 cm^{-1}; uv (ethanol) 229 nm (ϵ 8200); NMR (CCl_4) δ 1.35 (s, 9 H), 3.64 (s, 6 H), 3.68 (s, 3 H), 3.74 (s, 3 H), 6.61 (s, 1 H), 9.0 (s, 1 H, NH); mass spectrum (70 eV) *m/e* 357.1425 (calcd for $C_{16}H_{25}NO_8$, 357.1424); *m/e* (rel intensity) 358 (7), 357 (M^+, 40), 342 (5), 326 (7), 301 (14), 298 (3), 278 (5), 270 (7), 243 (10), 242 (100), 238 (18), 211 (8), 210 (82), 182 (5), 178 (15), 150 (7), 59 (12), 58 (3), 57 (25), 41 (18), 39 (3). Product **33** was independently synthesized by treating 210 mg (2.86 mmol) of *tert*-butylamine with 813 mg (5.70 mmol) of DMAD in dichloroethane at 90° for 16 hr. Chromatography on alumina using carbon tetrachloride elution and vacuum distillation (bp 106°, 0.1 mm) gave 840 mg (83%) of **33**.

Reaction of 32 and DMAD. A solution of 561 mg (2.61 mmol) of **32** and 372 mg (2.62 mmol) of DMAD was refluxed in dioxane for 24 hr and gave 658 mg (70%) of **33** after chromatography and vacuum distillation.

Attempted Reaction of Water and Adduct 2. Heating adduct **2** in aqueous dioxane for 24 hr produced no noticeable decomposition of **2** or formation of product **33.**

Attempted Reaction in Water and Imino Ether 6b. Heating imino ether **6b** in aqueous dioxane for 0.5 hr produced no noticeable reaction as ascertained by NMR. No reaction was detected on standing at room temperature for 2 days.

Hydrolysis of Imino Ether 1b. Heating 103 mg (0.80 mmol) of **1b** and 14.5 mg (0.80 mmol) of water in 1 ml of dioxane for 3 hr at 100° in a sealed NMR tube produced 42% of *N-tert*-butylformamide and 15% of *tert*-butylamine, with 42% unreacted **1b,** by NMR. No reaction was detected by NMR upon leaving imino ether **1b** with aqueous dioxane at room temperature for 16 hr.

Acknowledgment. We acknowledge the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work.

Registry No.—**1a,** 49680-36-6; **1b,** 55236-60-7; **2a,** 55236-61-8; **2b,** 55236-62-9; **6a,** 23974-38-1; **6b,** 23974-43-8; **7a,** 55236-63-0; **7b,** 55236-64-1; **8a,** 55236-65-2; **8b,** 55267-65-7; **12,** 52856-04-9; **13,** 55236-66-3; **14,** 55236-67-4; **15a,** 49680-46-8; **15b,** 23974-48-3; **16a,** 55236-68-5; **16b,** 55236-69-6; **17,** 55236-70-9; (*Z*)-**18,** 55236-71-0; (*E*)-**18,** 55236-72-1; **20a,** 5264-35-7; **20b,** 5264-35-7; **21,** 1120-64-5; **22,** 2525-16-8; **24,** 55236-73-2; **25a,** 55236-74-3; **25b,** 55236-75-4; **26,** 55236-76-5; **27,** 55236-77-6; **28,** 55236-78-7; **31,** 24427-31-4; **32,** 55236-58-3; **33,** 55236-59-4; DMAD, 762-42-5.

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Aromatic *N*-Oxides. IX. Reaction of *N*-Alkoxy-2- (and 4-) alkylpyridinium Salts with Base[1]

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Received February 27, 1975

The preparation of a number of *N*-benzyloxy- and *N*-*p*-nitrobenzyloxy-2- and 4-alkylpyridinium bromides and perchlorates are described. When these salts were treated with base, the decomposition products were primarily the corresponding alkylpyridines and benzaldehyde or *p*-nitrobenzaldehyde and in the case of the *N*-alkoxy-2-methyl- or 4-methylpyridinium salts 1-aryl-2-(2- or 4-pyridyl)ethanols **16–18** (ca. 25%) were also formed. Evidence is offered that formation of alcohols **16–18** proceeds via anhydro base **20** and **23** intermediates.

The reaction of aromatic *N*-oxides (e.g., pyridine *N*-oxide) with alkyl halides, alkyl sulfonates, or alkyl sulfates to produce *N*-alkoxy ammonium salts (e.g., *N*-methoxypyridinium methosulfate) has appeared in numerous reports in the literature.[3–14] These salts are known to undergo several types of reactions,[10] one of which is an alkaline decomposition to yield the corresponding nitrogen heterocycle and an aldehyde.[4–7,11–13] The initial report of this reaction