Photochemical Reactions of 4-Pyrimidones. Structures and Properties of the β-Lactams Formed

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The photochemistry of substituted 4-pyrimidone derivatives **1**, **3**, **5**, and **6** was studied in alcoholic solution. Upon irradiation, the fused 4-pyrimidones **1** and 2,3,6-trialkyl-4-pyrimidone **3** gave α-(aminoalkylidene)-β-alkoxy-β-lactams **2** and **4**, respectively. On the other hand, the substituted 4-pyrimidones **5** and **6** did not afford any products with properties expected of *N*-alkyl-2-azetidinone. The structure of **2a** was confirmed by X-ray crystallographic analysis. The geometrical isomerization about the double bond of the β-lactams obtained was also discussed.

In a preliminary communication,[1] we reported on the photochemical rearrangement of 6,7,8,9-tetrahydro-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one to 7-(aminoethylidene)-6-methoxy-8-oxo-1-azabicyclo[4.2.0]octane. The present work is an extension of this study to other 4-pyrimidone derivatives. This photochemical ring contraction of 4-pyrimidones offers a potentially useful synthetic pathway to β-lactams having an alkoxy group at the β position to the carbonyl group, and applications to the synthesis of several model compounds related to the penicillin and cephalosporin antibiotics[2] can be expected. With this prospect in mind, we have now investigated the photolysis of 4-pyrimidone derivatives in alcoholic solution.

Irradiation of Fused 4-Pyrimidones (1) and 2,3,6-Trialkyl-4-Pyrimidones (3) in Alcoholic Solution. Irradiation of **1a** in methanol under nitrogen with a high-pressure mercury lamp gave a single photoproduct **2a** in a yield of 66%. The NMR spectrum exhibited signals at δ 2.26 (s, 3 H) and 3.32 (s, 3 H), representing a methyl group and a methoxy group, respectively. The NMR spectrum also showed a broad singlet at δ 5.87 (s, 2 H) which, when considered with the stretching bands at 3430, 3360, and 3250 cm^{-1}, indicated a primary amino group. The IR bands at 1710 and 1690 cm^{-1} suggested a conjugated carbonyl group. Further inspection of the NMR spectrum of **2a** revealed the presence of a piperidine moiety at δ 1.07–1.94 (m, 5 H), 2.14–2.48 (m, 1 H), 2.53–2.93 (m, 1 H), and 3.67–3.98 (m, 1 H). From these data, the β-lactam structure **2a** was assigned.

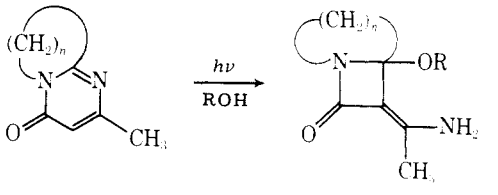
Analogous photolysis of either **1a** or **1b** in ethanol under nitrogen led to the formation of **2a'** and **2b'**, respectively, in 47–55% yield. Likewise, irradiation of **1b** and **3** in methanol solution gave **2b** and **4**, respectively (52–80%). The spectral data on these photoproducts also indicated β-lactam structures (Table I[3]). All compounds showed λ_{max} (MeOH) 272 ± 2 nm (ε 20 000). The infrared spectra (KBr) in each case showed three peaks of 3440–3220 and two at ~1700 and ~1690–1640 cm^{-1}.

To confirm the β-lactam structure and establish the molecular conformation, a direct X-ray analysis of **2a** was carried out. A stereoscopic view of the molecular structure found is shown in Figure 1. Bond lengths and angles are given in Figure 2. The molecular packing, atomic parameters, bond distances, bond angles, and displacement of the NCOC=CN plane of atoms appear in Figure 3 and Tables II–V.[3]

The molecular structure of **2a** is confirmed as 7-(aminoethylidene)-6-methoxy-8-oxo-1-azabicyclo[4.2.0]octane with the amino group oriented trans to the carbonyl group. The angular methoxy group is in an axial position. The relatively short C8–N1 distance (1.38 Å) is consistent with normal amide resonance.[4-6] The C9–N2 bond distance (1.35 Å) is much shorter than the normal C–N single bond (1.48 Å). This variation may be due to normal enamine resonance.[4a] In the crystal, the molecules are linked in chains by hydrogen-bond formation. The amine nitrogen atom is involved in two intermolecular hydrogen bondings; one to the carbonyl oxygen atom and the other to the methoxy oxygen atom, whose bond lengths are 2.97 and 3.07 Å, respectively.

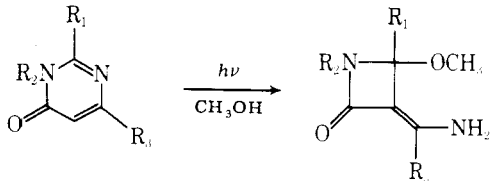
Careful reexamination of the NMR spectrum of **2a** in pyridine-d_5 solvent revealed new signals, δ 1.86 (s), 3.27 (s), and 6.17 (broad s), which gradually appeared after the solid β-lactam **2a** had been dissolved. The intensities of the new signals increased with the passage of time up to constant values while the intensities of the methyl, methoxy, and amine signals in the spectrum of **2a** decreased. The chemical shifts and intensities of the NMR signals assigned to the piperidine moiety of **2a** remained virtually unchanged. The new signals

Chart I



1a, *n* = 4
b, *n* = 5

2a, *n* = 4; R = CH_3
2a', *n* = 4; R = C_2H_5
2b, *n* = 5; R = CH_3
2b', *n* = 5; R = C_2H_5



3a–f **4a–f**

a, R_1 = CH_3; R_2 = CH_3; R_3 = CH_3
b, R_1 = CH_3; R_2 = C_2H_5; R_3 = CH_3
c, R_1 = CH_3; R_2 = *n*-C_3H_7; R_3 = CH_3
d, R_1 = CH_3; R_2 = $C_6H_5CH_2$; R_3 = CH_3
e, R_1 = C_2H_5; R_2 = CH_3; R_3 = CH_3
f, R_1 = CH_3; R_2 = CH_3; R_3 = C_2H_5

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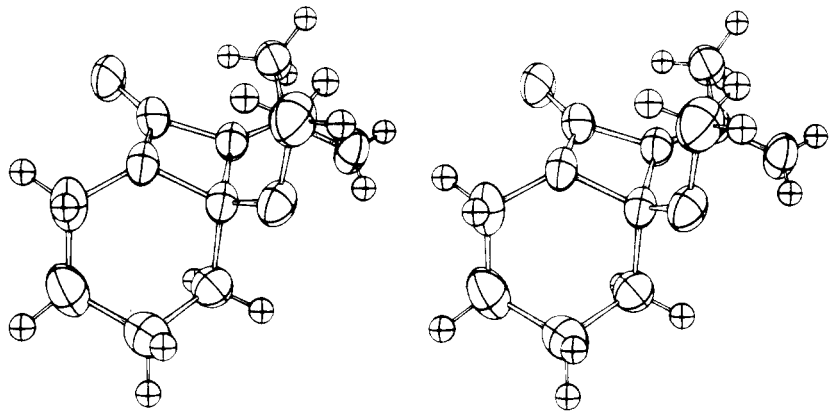


Figure 1. A stereoscopic view of the molecular conformation (**2a**).

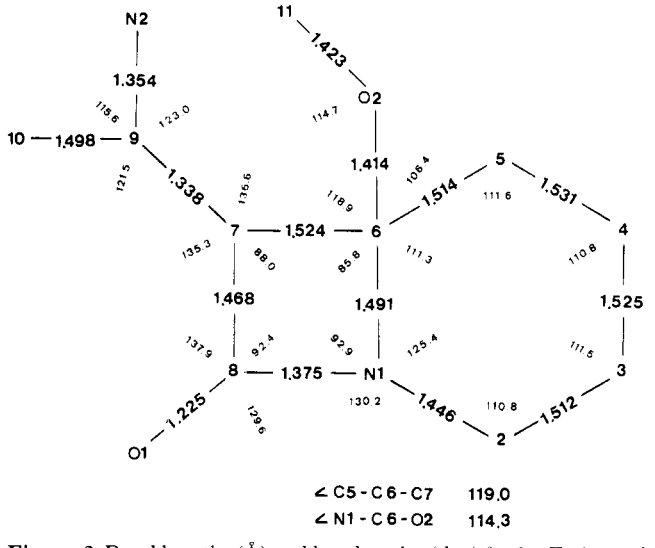


Figure 2. Bond lengths (Å) and bond angles (deg) for **2a**. Estimated standard deviations in bond distances are in the range 0.003–0.005 Å and in bond angles 0.2 to 0.3°.

were: δ 1.86 (s), 3.27 (s), and 6.17 (br, NH_2). When the solution was treated with D_2O, both the signal at δ 6.17 and the signal at δ 5.87 associated with the amine protons of **2a** disappeared immediately. These results suggest that **2a** in solution undergoes an isomerization about the double bond. Here, we define the trans and cis isomers of **2a** in terms of the relationship of the amino group to the carbonyl group. In the crystal, **2a** exists in the trans form *trans*-**2a**, which was determined by the X-ray analysis. Therefore, the NMR spectrum taken after about 10 min at 30 °C must be the signals of the trans isomer and the new signals (at δ 1.87, 3.27, and 6.17) correspond to those of the cis isomer *cis*-**2a**. The isomerization about the double bond of the β-lactam **2a** may occur via an imine intermediate such as **2a(Y)**.

After 4 h, these signals could be accounted for by the presence of an equilibrium mixture of *trans*-**2a** and its isomer *cis*-**2a** in solution. The ratio of *trans*-**2a** to *cis*-**2a** in equilibrium was expected to be a function of the stabilities of the β-lactam isomers in solution. The relative intensities of the signals ascribed to *trans*-**2a** and *cis*-**2a** were found to vary with both solvent and temperature. In pyridine-d_5 at 50 °C, the ratio of *trans*-**2a** to *cis*-**2a** was found to be 59:41, whereas in CD_3OD, Me_2SO-d_6, and $CDCl_3$ at 50 °C the ratios were 73:27, 65:35, and 49:51, respectively. The temperature dependence was shown by the ratios in pyridine-d_5 at 50, 0, and −24 °C, which were 59:41, 61:39, and 63:37 (experimental error 1%), respectively.

Table VI. Equilibrium Ratios of the Trans to Cis Isomers of the β-Lactams in the Pyridine-d_5 at 50 °C

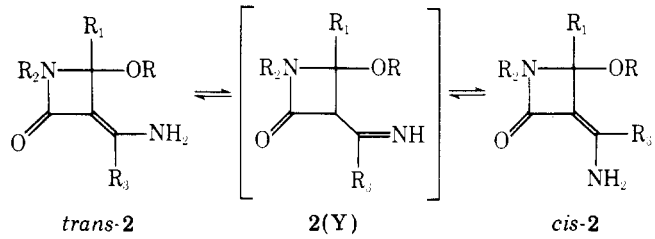
β-lactam	% trans	% cis
2a	59	41
2a'	61	39
2b	66	34
2b'	64	36
4a	67	33
4b	65	35
4c	65	35
4d	65	35
4e	64	36
4f	68	32

Similarly, in the case of the β-lactams (**2a', 2b, 2b'**, and **4**), the respective NMR spectra also indicated the signals corresponding to both the trans and cis isomers in pyridine-d_5 at 50 °C.[3] Equilibrium ratios (trans/cis) of **2** and **4** in pyridine-d_5 at 50 °C are shown in Table VI. On the basis of the NMR spectral data, **2** and **4** were shown to have the amino group located *trans* to the carbonyl group in the crystal. Analogous isomerization about the double bond of some amino vinyl ketones was observed by Dudek and Volpp.[7]

Mechanism. The photochemical reactions of 4-pyrimidone derivatives, **1** and **3**, may be described by the reaction in Scheme II.

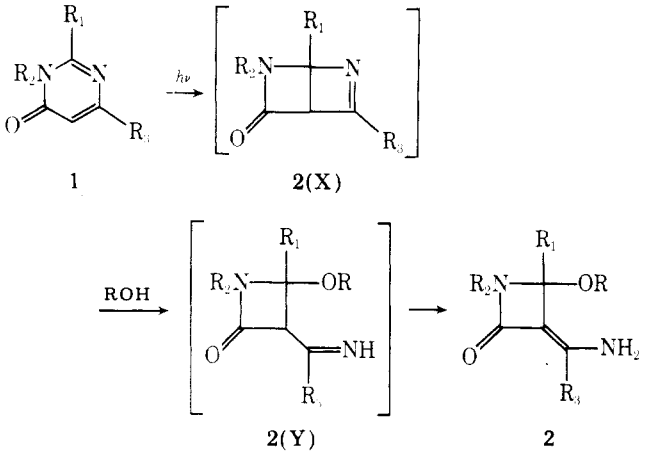
Electrocyclic reactions of cisoid diene systems in excited states are symmetry allowed for the disrotatory mode of ring

Scheme I



2a, R_1 and R_2 = $-(CH_2)_4-$; R_3 = CH_3; R = CH_3
a', R_1 and R_2 = $-(CH_2)_4-$; R_3 = CH_3; R = C_2H_5
b, R_1 and R_2 = $-(CH_2)_5-$; R_3 = CH_3; R = CH_3
b', R_1 and R_2 = $-(CH_2)_5-$; R_3 = CH_3; R = C_2H_5
4a, R_1 = CH_3; R_2 = CH_3; R_3 = CH_3; R = CH_3
b, R_1 = CH_3; R_2 = C_2H_5; R_3 = CH_3; R = CH_3
c, R_1 = CH_3; R_2 = n-C_3H_7; R_3 = CH_3; R = CH_3
d, R_1 = CH_3; R_2 = $C_6H_5CH_2$; R_3 = CH_3; R = CH_3
e, R_1 = C_2H_5; R_2 = CH_3; R_3 = CH_3; R = CH_3
f, R_1 = CH_3; R_2 = CH_3; R_3 = C_2H_5; R = CH_3

Scheme II



closure.[8] Irradiation of **1** or **3** gives an excited molecule which, upon cyclization, would give the intermediate **X.** Analogous electrocyclic reactions have been observed in the photochemistry of 2-pyrimidinones, tetramethylpyrazinone, and 2-pyridones.[9-11]

Irradiation of **1a** in methanol under an aerated atmosphere (bubbling dry air through the reaction) was carried out. The isolated amount of **2a** was constant within the experimental error (about 15% in the experimental conditions used). This result suggests that the photochemical cyclization may occur from the π,π^* singlet state of **1a.** However, there remains a possibility that molecular oxygen would not quench the triplet state of **1a** because of the short triplet lifetime.

The photolysis of **1a** in cyclohexane at 40 °C was carried out in order to obtain more information about the reaction mechanism. Attempts to isolate the intermediate **2a(X)** were unsuccessful. However, the photolyzed mixture, when treated with either methanol or ethanol after irradiation, afforded **2a** (13% isolated yield, 46% by NMR) and **2a'** (6.4% isolated yield, 38% by NMR), respectively. This result shows that the initial photoproduct should be the intermediate **2a(X)** which reacts with alcohol to give the imine intermediate **2a(Y).**[13]

The tautomerization of the imine to the enamine is assumed in Scheme I to explain our observations of the trans-cis isomerization about the double bond of the β-lactams. In imine–enamine tautomerization of some vinyl amines, the ratios of the imine to the enamine in equilibrium were found to vary with both solvent and temperature.[14] Hence, **2** and **4** should be more stable than **2(Y)** and **4(Y),** in the experimental conditions used.

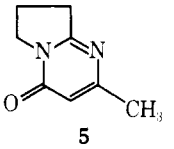
Finally, it should be noted that irradiation of **5** and **6** in methanol solution did not give the corresponding β-lactams. The starting materials were recovered for **5** and **6a–d.** 4-Pyrimidone **6e** afforded only a polymeric product, and **6f** afforded no separable product. The absence of β-lactams from compounds **5** and **6** suggests that little or no photochemical cyclization occurs for these compounds.

Experimental Section

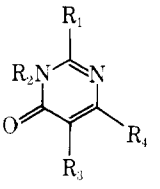
Melting points were measured with Yanako micromelting-point apparatus and are uncorrected. To determine IR and UV spectra, 215 Hitachi Grating Infrared and Hitachi Model 200-01 spectrophotometers were used respectively. The ^{1}H NMR spectra were taken on a Varian EM-390 90-MHz spectrometer and are reported in parts per million downfield from tetramethylsilane. Mass spectra were measured with a JEOL-OISG-2 spectrometer. Column chromatography was performed on alumina (Merck CO., Ltd.).

Materials. 2,3,6-Trimethyl-4-pyrimidone (**3a**), 3-ethyl-2,6-dimethyl-4-pyrimidone (**3b**), and 2-ethyl-3,6-dimethyl-4-pyrimidone (**3e**) were prepared as described in the literature.[15,16] 6,7,8,9-Tetrahydro-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**1a**) was synthesized by condensation of 2-amino-3,4,5,6-tetrahydropyridine hydrochloride with methyl acetoacetate as described in the literature.[17] Recrystallization from benzene gave **1a** with mp 80–83 °C (lit.[18] mp 80–83 °C).[18] 6,7,8,9,10-Pentahydro-2-methyl-4*H*-pyrido[1,2-*a*]azepin-4-one (**1b**) was prepared from caprolactamamidine hydrochloride and methyl acetoacetate as described in the literature.[19] Recrystallization from ethanol–ether gave **1b** with mp 83.5–85 °C (lit.[19] mp 84.5–86.5 °C).[19] 2,3-Dimethyl-3-propyl-4-pyrimidone (**3c**), 3-benzyl-2,3-dimethyl-4-pyrimidone (**3d**), and 6-ethyl-2,3-dimethyl-4-pyrimidone (**3f**) were prepared from the corresponding alkyl halides and pyrimidine derivatives[20] in dimethylformamide solvent containing sodium methoxide at room temperature, respectively.

Chart II



5



6a, $R_1 = CH_3$; $R_2 = H$; $R_3 = H$; $R_4 = CH_3$
b, $R_1 = H$; $R_2 = CH_3$; $R_3 = CH_3$; $R_4 = CH_3$
c, $R_1 = CH_3$; $R_2 = C_6H_5$; $R_3 = H$; $R_4 = CH_3$
d, $R_1 = SCH_3$; $R_2 = CH_3$; $R_3 = H$; $R_4 = CH_3$
e, $R_1 = CH_3$; $R_2 = CH_3$; $R_3 = CH_3$; $R_4 = CH_3$
f, $R_1 = C_6H_5$; $R_2 = CH_3$; $R_3 = H$; $R_4 = CH_3$

For **3c:** mp 59–61 °C; IR (KBr) 1670 cm^{-1}; NMR ($CDCl_3$) δ 1.00 (t, J = 8.0 Hz, 3 H), 1.40–2.00 (m, 2 H), 2.18 (s, 3 H), 2.55 (s, 3 H), 3.93 (t, J = 8.0 Hz, 2 H), 6.05 (s, 1 H); MS *m/e* 166 (M^+).

Anal. Calcd for $C_9H_{14}N_2O$: C, 65.03; H, 8.49; N, 16.85. Found: C, 65.30; H, 8.54; N, 17.08.

For **3d:** mp 36–37 °C; IR (KBr) 1680 cm^{-1}; NMR ($CDCl_3$) δ 2.17 (s, 3 H), 2.32 (s, 3 H), 5.15 (s, 2 H), 6.06 (s, 1 H), 7.20 (s, 5 H); MS *m/e* 214 (M^+).

Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08. Found: C, 72.83; H, 6.47; N, 13.37.

For **3f:** bp 134–135 °C (15 torr); IR (Nujol) 1660 cm^{-1}; NMR ($CDCl_3$) δ 1.17 (t, J = 6.0 Hz, 3 H), 2.39 (q, J = 6.0 Hz, 2 H), 2.50 (s, 3 H), 3.53 (s, 3 H), 5.90 (s, 1 H); MS *m/e* 152 (M^+).

Anal. Calcd for $C_8H_{12}N_2O$: C, 63.13; H, 7.95; N, 18.41. Found: C, 63.32; H, 8.05; N, 18.17.

General Procedures for the Irradiation of 4-Pyrimidones 1 and 3 in Alcoholic Solution and for the Isolation of the Photoproducts 2 and 4. The respective 4-pyrimidone (1.9–3.0 g) was dissolved in 320 mL of alcohol (methanol or ethanol) in a reaction cell. The solution was stirred magnetically and degassed with nitrogen for 0.5 h. The solution was irradiated with a Nikko Seiki 200-W high-pressure mercury lamp equipped with a quartz tube immersed in the reaction cell at 30–35 °C. Reaction progress was routinely followed by thin-layer chromatography (TLC). TLC analysis [alumina plate with benzene–ethyl acetate (1:1 mixture by volume) developer] showed the decrease of the starting material and the appearance of a new spot. To avoid further photochemical decomposition of the product, the irradiation was terminated when the spots of byproducts were clearly observed. After irradiation, the solvent was removed by rotary evaporation. Benzene or ether was added to the oily residue. On cooling, crude crystals were separated and collected by filtration. Removal of the solvent under vacuum from the mother liquor followed by addition of enough ether and of a small amount of *n*-hexane to effect solution (about 5 mL) and storage in the freezer for 2 days yielded an additional amount of crude crystals. The starting material was recovered by column chromatography of the filtrate on alumina using benzene as an eluent.

7-(Aminoethylidene)-6-methoxy-8-oxo-1-azabicyclo[4.2.0]-octane (2a). From 2.31 g of **1a** in methanol, 1.27 g of **2a** was obtained after 3.5 h of irradiation. The starting material (**1a,** 0.69 g) was recovered. The conversion yield of **2a** was 66%. Recrystallization of **2a** from methanol gave colorless prisms.

7-(Aminoethylidene)-6-ethoxy-8-oxo-1-azabicyclo[4.2.0]octane (2a'). From 2.43 g of **1a** in ethanol, 0.81 g of **2a'** was obtained

Table VII. Melting Point, Analytical Data, and Molecular Ion (Mass Spectrum)[a]

compd	mp, °C	molecular ion (*m/e*)
(2a) $C_{10}H_{16}N_2O_2$	178–180	196
(2a') $C_{11}H_{18}N_2O_2$	142–143	210
(2b) $C_{11}H_{18}N_2O_2$	127–129	210
(2b') $C_{12}H_{20}N_2O_2$	143–145	224
(4a) $C_8H_{14}N_2O_2$	131–132	170
(4b) $C_9H_{16}N_2O_2$	112–114	184
(4c) $C_{10}H_{18}N_2O_2$	93–95	198
(4d) $C_{14}H_{18}N_2O_2$	104–105	246
(4e) $C_9H_{16}N_2O_2$	113–115	184
(4f) $C_9H_{16}N_2O_2$	90–91	184

[a] Satisfactory analytical data (±0.3% for C, H, N) were reported for all compounds in the table.

after 3.5 h of irradiation. The starting material (**1a**, 1.27 g) was recovered. The conversion yield of **2a'** was 55%. Recrystallization of **2a'** from ethanol gave colorless prisms.

8-(Aminoethylidene)-7-methoxy-9-oxo-1-azabicyclo[5.2.0]nonane (2b). From 2.09 g of **1b** in methanol, 1.16 g of **2b** was obtained after 2 h of irradiation. The starting material (**1b**, 0.53 g) was recovered. The conversion yield of **2b** was 63%. Recrystallization of **2b** from methanol–ether gave colorless prisms.

8-(Aminoethylidene)-7-ethoxy-9-oxo-1-azabicyclo[5.2.0]nonane (2b'). From 2.32 g of **1b** in ethanol, 0.78 g of **2b'** was obtained after 3.5 h of irradiation. The starting material (**1b**, 1.00 g) was recovered. The conversion yield of **2b'** was 47%. Recrystallization of **2b'** from methanol–ether gave colorless prisms.

***N*-Methyl-3-(aminoethylidene)-4-methoxy-4-methyl-2-azetidinone (4a).** From 2.10 g of **3a** in methanol, 0.89 g of **4a** was obtained after 3 h of irradiation. The starting material (**3a**, 0.85 g) was recovered. The conversion yield of **4a** was 58%. Recrystallization of **4a** from methanol–ether gave colorless prisms.

***N*-Ethyl-3-(aminoethylidene)-4-methoxy-4-methyl-2-azetidinone (4b).** From 1.92 g of **3b** in methanol, 0.67 g of **4b** was obtained after 3.5 h of irradiation. The starting material (**3b**, 0.90 g) was recovered. The conversion yield of **4b** was 54%. Recrystallization of **4b** from methanol–ether gave colorless prisms.

***N*-Propyl-3-(aminoethylidene)-4-methoxy-4-methyl-2-azetidinone (4c).** From 2.00 g of **3c** in methanol, 0.93 g of **4c** was obtained after 3 h of irradiation. The starting material (**3c**, 0.64 g) was recovered. The conversion yield of **4c** was 57%. Recrystallization of **4c** from methanol–ether gave colorless prisms.

***N*-Benzyl-3-(aminoethylidene)-4-methoxy-4-methyl-2-azetidinone (4d).** From 2.32 g of **3d** in methanol, 1.21 g of **4d** was obtained after 3 h of irradiation. The starting material (**3d**, 0.31 g) was recovered. The conversion yield of **4d** was 52%. Recrystallization of **4d** from methanol–ether–*n*-hexane gave colorless prisms.

***N*-Methyl-3-(aminoethylidene)-4-ethyl-4-methoxy-2-azetidinone (4e).** From 2.07 g of **3e** in methanol, 0.71 g of **4e** was obtained after 3 h of irradiation. The starting material (**3e**, 1.00 g) was recovered. The conversion yield of **4e** was 55%. Recrystallization of **4e** from methanol–ether gave colorless crystals.

***N*-Methyl-3-(1-aminopropylidene)-4-methoxy-4-methyl-2-azetidinone (4f).** From 3.00 g of **3f** in methanol, 0.80 g of **4f** was obtained after 4 h of irradiation. The starting material (**3f**, 2.71 g) was recovered. The conversion yield of **4f** was 80%. Recrystallization of **4f** from methanol–ether–*n*-hexane gave colorless crystals.

Melting points, analytical data, and molecular ions (mass spectrum) are given in Table VII. The full NMR data are summarized in Tables VIII and IX.[3]

Crystal Data: $C_{10}H_{16}N_2O_2$, M = 196.25, monoclinic, a = 13.518 (5) Å, b = 10.688 (5) Å, c = 7.382 (3) Å, β = 95.71 (3)°, U = 1061.2 Å^3, D_c = 1.23 g cm^{-3}, Z = 4, $F(000)$ = 396, Cu Kα radiation 1.5418 Å (monochromated by a graphite plate); μ(Cu Kα) = 6.97 cm^{-1}, space group $P2_1/a$ (from systematic absence). A single crystal of **2a** suitable for X-ray diffraction study was grown from a methanol solution. Cell dimensions were determined from Weissenberg and Precession photographs and refined by the least-squares method using 20 2θ values accurately measured on a computer-controlled four-circle diffractometer AFC/3 (RIGAKU).

Intensity Data Collection. Three-dimensinal intensity data were obtained for a prismatic crystal with dimensions of 0.4 × 0.4 × 0.6 mm, aligned with its c axis along the ϕ axis of the diffractometer. All reflections with $2\theta < 120°$ were measured by using the $\omega/2\theta$ scan technique. No significant changes in the measurement of the intensities of three standard reflections monitored every 52 scans were observed during the course of data collection. Scattered intensity significantly above background [$|F_o| > 2.5\sigma(|F_o|)$] was found at 1263 of the 1738 independent locations surveyed. No absorption corrections were made.

Structure Determination and Refinement. The structure was solved by routine application of the program MULTUN[21] using the $181E(hkl) > 1.60$. An E map computed from the phase set with the highest figure of merit (1.233) revealed all nonhydrogen atoms. The structure was refined by the block-diagonal least-squares methods. The quantity minimized was $\Sigma w(|F_o| - |F_c|)^2$. Hydrogen atoms were located by three-dimensional differance Fourier maps. In the final cycles of the least-squares refinement, the anisotropic thermal factors for nonhydrogen atoms and isotropic thermal factors for hydrogen atoms were used. The refinement was terminated when all shifts were less than 0.2σ. In this refinement cycle, four reflections, (−1,1,1), (0,0,1), (0,2,1), and (0,0,2), were deleted because these reflections were considered to be measured wrong in view of the counting statistics. The final agreement factors are: $R = \Sigma(|F_o|^2 - |F_c|^2)/(\Sigma|F_o|^2) = 0.053$, $R_w = [\Sigma w(|F_o| - |F_c|)^2/\Sigma w|F_o|^2]^{1/2} = 0.068$. The weighting scheme was: $W^{-1} = 0.46057 - 0.03106|F_o| + 0.00305|F_o|^2$, which was deduced from the $\langle\Delta|F|\rangle$ vs. $|F_o|$ distribution.

The atomic scattering factors were taken from the International Tables for X-Ray Crystallography.[22]

The refined crystallographic structure was stereographically plotted (Figure 1) using the ORTEP computer program.[23]

Registry No.—**1a**, 58156-40-4; **1b**, 69912-22-7; *cis*-**2a**, 69912-23-8; *trans*-**2a**, 69912-24-9; *cis*-**2a'**, 69912-25-0; *trans*-**2a'**, 69912-26-1; *cis*-**2b**, 69912-27-2; *trans*-**2b**, 69912-28-3; *cis*-**2b'**, 69912-29-4; *trans*-**2b'**, 69912-30-7; **3a**, 32363-51-2; **3b**, 32363-52-3; **3c**, 69912-31-8; **3d**, 69912-32-9; **3e**, 32363-54-5; **3f**, 69912-33-0; *cis*-**4a**, 69912-34-1; *trans*-**4a**, 69912-35-2; *cis*-**4b**, 69912-36-3; *trans*-**4b**, 69912-37-4; *cis*-**4c**, 69912-38-5; *trans*-**4c**, 69912-39-6; *cis*-**4d**, 69912-40-9; *trans*-**4d**, 69912-41-0; *cis*-**4e**, 69912-42-1; *trans*-**4e**, 69912-43-2; *cis*-**4f**, 69912-44-3; *trans*-**4f**, 69912-45-4; 2,6-dimethyl-4(1*H*)-pyrimidinone, 6622-92-0; 6-ethyl-2-methyl-4(1*H*)-pyrimidinone, 52421-75-7; methanol, 67-56-1; ethanol, 64-17-5.

Supplementary Material Available: Atomic parameters for the nonhydrogen atoms and hydrogen atoms, bond distances, bond angles, displacements of the NCOC=CN plane of the atoms, molecular packing, and full NMR data for compounds **2** and **4** (Tables I–V, VIII, and IX and Figure 3) (9 pages). Ordering information is given on any current masthead pages.

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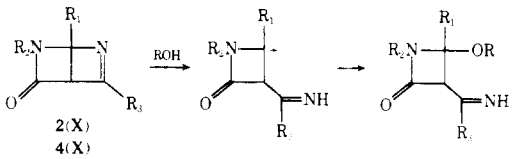

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Selectivity of Attack in Nucleophilic Alkylation of Nitroarenes with Grignard Reagents. Reactivity of Some Substituted Nitrobenzenes and Nitronaphthalenes

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Reactivity of some substituted nitrobenzenes and nitronaphthalenes with RMgX has been investigated. In all reactions C-alkylation products have been obtained. The entering alkyl group exhibits a great tendency to attack at unsubstituted positions. Examples of nucleophilic displacement of a nucleofugic group by an alkyl group are also reported. Our findings are discussed and compared with analogous studies on relative reactivities of differently substituted aromatic carbons toward nucleophiles. Anomalous behavior has been observed for reactions of methoxy derivatives which yield nitrocyclohexadienic or cyclohexenic compounds and lesser amounts of the expected nitroso derivatives. This unusual reactivity can be accounted for by a rapid aci–nitro tautomerization which prevails over decomposition to nitroso compounds.

It has been accepted[2] for a long time that the action of any type of Grignard Reagents on mononitroarenes could exclusively lead to N-alkylation products through 1,2 addition to the nitro group. Examples[3] of conjugate addition were confined to polynitro compounds.

We recently reported[4] that treatment of mononitroarenes with alkylmagnesium halides results in nucleophilic alkylation at ortho or para positions. Thus, the reactivity of alkyl and aryl[5] reagents has now been differentiated.

Our reaction is thought[6] to proceed through a conjugate addition (1,4 or 1,6) of RMgX to the nitroarenic system leading to adducts whose structure are similar to those postulated by Bunnett[7] for σ-anionic intermediates in nucleophilic aromatic substitution. The adducts can be decomposed to alkylnitroso compounds by adding concentrated hydrochloric acid or boron trifluoride.

Our results are strongly supported by a recent paper[8] in which this type of reactivity is extended to lithium alkyl compounds.

More recently we started studying the possibility of alkylating the substituted aromatic carbon. In a short paper,[9] we reported that the presence of a methyl group in *p*-methylnitrobenzene does not prevent attack of the entering alkyl group at the para position.

These interesting preliminary results prompted us to examine the influence of substituents on reactivity. In this paper we report the results obtained with reactions of some substituted nitrobenzenes and nitronaphthalenes.

Results

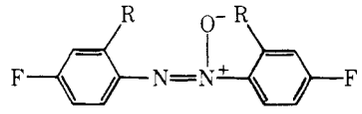
Reactivity of nitrobenzene (**1**) and *p*-phenoxy (**2**), *p*-(phenylthio) (**3**), *p*-(methylthio) (**4**), *p*-fluoro (**5**), *p*-chloro (**6**), *p*-methoxy (**7**), and *p*-(*N*,*N*-dimethylamino) derivatives with methyl- (**a**), *n*-butyl- (**b**), (2-phenylethyl)- (**c**), *sec*-butyl- (**d**), and benzyl- (**e**) magnesium halides in tetrahydrofuran or diethyl ether was investigated. Similar studies were performed on 1-nitro-2-methoxy- (**8**) and on 1-methoxy-2-nitro (**9**) naphthalenes.

Each experiment was performed with the same experimental procedure used for *p*-methylnitrobenzene,[9] which utilizes concentrated hydrochloric acid (33%) to decompose the adducts.

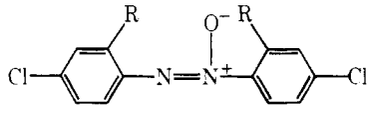
Investigated reactions and isolated products are summarized in Table I. The reported yields are those of pure products, obtained through chromatographic separation on silica gel columns, except for **1** for which the overall yield is given. This was calculated based on the mixture of both isomers **10** and **11** after preliminary purification from tars and other secondary products. ^{1}H-NMR analysis of this mixture gives approximately a 2:1 ratio value for ortho/para alkylation.

For the whole series of *p*-Z-nitrobenzenes, with the exception of **7**, the main reaction product is a 2-alkyl-4-Z-nitrosobenzene.

Reactions are often accompanied by formation of tars and trace amounts of byproducts, mainly arising from decomposition of nitroso derivatives (azoxy, nitro, etc.). In the reactions of **5** and **6**, the presence of azoxy compounds in the reaction products is considerable. They have been identified as 2,2′-dialkyl-4,4′-difluoro- (**17**) and 2,2′-dialkyl-4,4′-dichloro- (**18**) azoxybenzenes, respectively.



17a, R = CH_3
b, R = *n*-C_4H_9



18c, R = $PhCH_2CH_2$

Under identical experimental conditions, **7** yields mainly 1-nitro-4-methoxy-6-alkyl-1,3-cyclohexadiene (**19**) and lesser amounts of the expected nitroso compound (**20**). Similar re-

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