+ 1)$^+$, calcd for $C_{16}H_{23}O_3$ 263.1647]. For **14**: IR 2970 (m), 1725 (s), 1716 (s), 1645 (w), 1575 (m), 1375 (m), 1155 (s) cm^{-1}; NMR δ 7.46 (d, J = 5.7 Hz, 1 H), 6.14 (d, J = 5.7 Hz, 1 H), 6.10 (ddd, J = 7.3, 7.3, 11.6 Hz, 1 H), 5.76 (ddd, J = 1.8, 1.8, 11.5 Hz, 1 H), 2.97 (ddd, J = 1.81, 7.0, 16.1, 1 H), 2.74 (ddd, J = 1.5, 7.5, 16.4 Hz, 1 H), 2.56 (d, J = 19.2 Hz, 1 H), 2.24 (d, J = 19.2 Hz, 1 H), 1.48 (s, 9 H), 1.43 (d, J = 5.5, 1 H), 1.42 (d, J = 5.6, 1 H), 1.19 (s, 3 H); mass spectrum, m/z 263.1713 [(M + 1)$^+$, calcd for $C_{16}H_{23}O_3$ 263.1647].

B. Formation of 12 in Benzene Containing $NaHCO_3$. Thermolysis of **8b** as above in benzene, but containing solid $NaHCO_3$ (stirred, sealed ampule) yielded **12** as before, but no **14**.

C. Formation of 20 in Methanol. Thermolysis of **8b** (5.0 mg) as above, but in methanol (1.75 mL) containing $NaHCO_3$ (50 mg), yielded **20** (50%), which was identified by comparison with the photochemically produced material described below.

Thermolysis of *tert*-Butyl 1-Methyl-5-oxo[4.4.4.5]fenestrane-7α-carboxylate (9b). A solution of **9b** (7 mg) in benzene (1 mL) containing $NaHCO_3$ was heated 20 h at 100 °C. Flash chromatography yielded one product identified as **13** (1 mg) from its spectra: NMR δ 7.45 (d, J = 16.2 Hz, 1 H), 6.27 (d, J = 0.6 Hz, 1 H), 6.26 (d, J = 16.1 Hz, 1 H), 4.86 (d, J = 0.8 Hz, 1 H), 4.74 (d, J = 0.6 Hz, 1 H), 3.37-3.26 (br m, 1 H), 2.60 (dd, J = 6.5, 18.9 Hz, 1 H), 2.30 (dd, J 1.3, 18.9 Hz, 1 H), 1.95-1.85 (m, 2 H), 1.77 (s, 3 H), 1.53 (s, 9 H); mass spectrum, m/z 262.1586 (M$^-$, calcd for $C_{16}H_{22}O_3$ 262.1569).

Photolysis of 8b. A solution of **8b** (0.011 g) in benzene (2 mL), methanol (0.15 mL), and K_2CO_3 (0.002 g) was degassed and irradiated through Pyrex with a 450-W Hanovia mercury lamp. Reaction was closely monitored by TLC and found to be complete in 5 h. Solvent was removed, and the residue was purified by flash chromatography (20% ether in hexane) to obtain three products: **28**, 0.004 g (36%); **20**, 0.0006 g (5%); **21**, 0.0006 g (5%). For **20**: IR 1738, 1711 cm^{-1}; NMR δ 6.23 (dt, J = 7.5, 11.6 Hz, 1 H), 5.82 (dt, J = 1.41, 11.9 Hz, 1 H), 3.21 (s, 3 H), 3.11 (ddd, J = 1.1, 7.37, 15.34 Hz, 1 H), 2.88-2.99 (m, 3 H), 2.74 (d, J = 19.4, 1 H), 2.56 (d, J = 20.95 Hz, 1 H), 2.53 (dd, J = 1.44, 18.13 Hz, 1 H), 2.16 (dd, J = 9.53, 12.1 Hz, 1 H), 1.49 (s, 9 H), 1.06 (s, 3 H), 0.82 (dd, J = 8.16, 11.97 Hz, 1 H); mass spectrum, m/z 293.1740 [(M - H)$^-$, calcd for $C_{17}H_{25}O_4$ 293.1753]. For **21**: NMR δ 6.92 (dt, J = 7.7, 15.5 Hz, 1 H), 5.83 (dt, J = 1.2, 15.4 Hz, 1 H), 3.19 (s, 3 H), 2.89 (dd, J = 17.13, 8.55 Hz, 1 H), 2.73 (d, J = 19.48, 1 H), 2.57 (d, J = 8.52 Hz, 1 H), 2.51-2.58 (m, 1 H), 2.51 (dd, J = 1.40, 7.96 Hz, 1 H), 2.40 (dd, J = 7.71, 14.26 Hz, 1 H), 2.15 (d, J = 18.64 Hz, 1 H), 2.07 (dd, J = 9.61, 12.26 Hz, 1 H), 1.49 (s, 9 H), 1.05 (s, 3 H), 0.84 (dd, J = 8.35, 12.21, 1 H); mass spectrum, m/z 293.1740 [(M - H)$^-$, calcd for $C_{17}H_{25}O_4$ 293.1753]. For **28**: ^{1}H and ^{13}C NMR spectra given in the text; IR 3061 (w), 2979 (s), 2930 (s), 2819 (w), 2717 (w), 1725 (s), 1456 (m), 1392 (m), 1368 (m), 1151 (s), 1124 (m), 909 (s) cm^{-1}; mass spectrum, m/z 263.1649 [(M + 1)$^+$, calcd for $C_{16}H_{23}O_3$ 263.1647].

Acknowledgment. We thank the National Science Foundation for support of this research, Laura Mieszerski and Lori Gentile for technical assistance, and Francis Picart, Susan Meyer, and Julie Wu for NMR spectra, which were determined on a spectrometer purchased with funds from the National Science Foundation, the National Institutes of Health, and the Keck Foundation. Mass spectral analyses were performed by The Rockefeller University Mass Spectrometric Biotechnology Resource on a VG-70250 magnetic sector instrument.

Supplementary Material Available: ORTEP diagrams of **11** and the 2,4-dinitrophenylhydrazone of **14** and listings of atomic coordinates, bond lengths, bond angles, anisotropic parameters, and H atom coordinates and isotropic parameters for **11** and of distances and angles for the 2,4-dinitrophenylhydrazone of **14** (12 pages). Ordering information is given on any current masthead page.

Two Triplets Mediating Intramolecular Photochemical Abstraction of Hydrogen by Nitrogen in 4-Acyl-6-alkylpyrimidines

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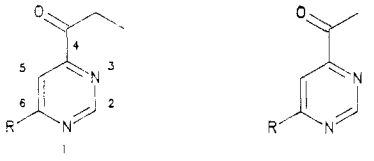
Contribution from the Laboratories of The Rockefeller University, New York, New York 10021-6399. *Received March 14, 1988*

Abstract: Direct irradiation with λ >340 nm of 4-acyl-6-alkylpyrimidines **1a** and **2c** or their triplet sensitization by aromatic ketones leads to an nπ* triplet (E_T ~ 70-71 kcal/mol). In **1a** this state is responsible for hydrogen abstraction from the C(4) side chain and isomerization to cyclopropanol **3** (eq 1). Ketone **2c** does not fragment under either these direct or sensitized conditions. However, triplet sensitization of **2c** by acetone (E_T ~ 79-82 kcal/mol) or direct irradiation of **2c** through Vycor, λ >200 nm, leads to hydrogen abstraction, cleavage of the C(6) side chain, and formation of **2a** (eq 2) in a reaction occurring from an upper nπ* triplet (E_T ~ 79-84 kcal/mol). Ketone **1c** yields mainly **5** and, depending upon conditions, a small amount of **1a** or **3** or both; the minor products arise by a novel monophotonic pathway (see eq 4).

We have found that in 4-acyl-6-alkylpyrimidines such as **1** and **2** intramolecular abstraction of hydrogen by nitrogen occurs from two distinct triplet states differing in energy by ~10 kcal/mol and that each of these states may be reached by appropriate triplet sensitization or direct irradiation. Despite its fundamental nature and biological implications,[1] photochemical abstraction of hydrogen by aromatic nitrogen has received much less attention than the related abstraction by carbonyl oxygen.[2] One complexity characteristic of functionalized nitrogen heteroaromatics is the



1 2

a, R = CH_3

b, R = H

c, R = $CH_2CH_2CH(CH_3)_2$

(1) Jagger, J. *Photochem. Photobiol. Rev.* **1983**, *7*, 1. Hall, J. D.; Mount, D. W. *Prog. Nucleic Acid Res.* **1981**, *25*, 53. Smith, K. C. *Aging, Carcinogenesis, and Radiation Biology*; Plenum: New York, 1976. Harm, W. *Biological Effects of Ultraviolet Radiation*; Cambridge University Press: London, 1980.

(2) A review covering both reactions is available: Wagner, P. J. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic: New York, 1980; Vol. 3, Chapter 20. For more recent reports of hydrogen abstraction by nitrogen in 2(1*H*)-pyrimidinones, see the following: Nishio, T.; Katahira, K.; Omote, Y. *Chem. Lett.* **1982**, 1675. Nishio, T.; Kameyama, S.; Omote, Y. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1147. Photochemical electron-transfer reactions of nitrogen aromatics and related imine systems have received much greater attention and have been reviewed recently: Mariano, P. S. *Org. Photochem.* **1987**, *9*, 1.

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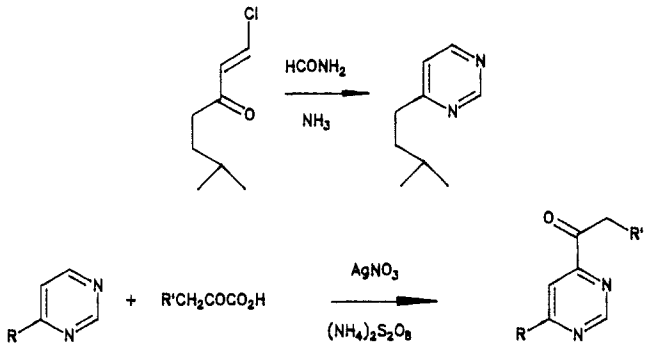
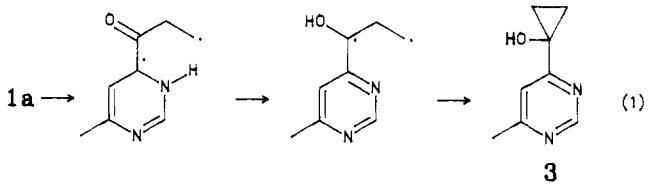
Scheme I



large number of electronic excited states available. For example, pyridines, which are the only group that has been examined in detail, have one $\pi\pi^*$ and two $n\pi^*$ triplets in the range 75–85 kcal/mol; one of the $n\pi^*$ states has its spin density localized partly on nitrogen and one on C(2) and C(6); and the ordering, energies, and spectroscopic behavior of all three states are sensitive functions of the position and nature of the substituents on the pyridine ring.[3] Asymmetrically substituted pyrimidines such as **1** and **2** can be expected then to possess an even more extensive array of triplets. Reactions from upper excited states continue to be of general interest,[4] and to the best of our knowledge the work reported here provides the first evidence for chemical reactivity from an upper triplet of this type. With this in mind, we have explored the photochemistry of **1a**, **2c**, and **1c**, where the site of intramolecular hydrogen abstraction through a six-membered intermediate can be, respectively, N(3), N(1), and both nitrogen atoms.

Preparative Experiments. Ketones **1a** and **2c** were accessible through free-radical acylation of the corresponding 4-alkylpyrimidine. For **2c**, 4-isopentylpyrimidine was acetylated on treatment with pyruvic acid, silver nitrate, and ammonium peroxysulfate.[5,6] For introduction of a propionyl group we found that this procedure could be extended to include the use of α-ketobutyric acid in place of pyruvic acid, and this then served for preparation of **1a** and **1c**. 4-Isopentylpyrimidine was prepared by condensation of 1-chloro-6-methyl-1-hepten-3-one[7] with formamide, following a known general procedure;[8] 4-methylpyrimidine is commercially available. These transformations are summarized in Scheme I. Products **1a**, **1c**, and **2c** were carefully purified by preparative gas chromatography before irradiation, since their photochemical behavior was unusually sensitive to contaminants; irradiation of impure compounds led to dark solutions and involatile products.

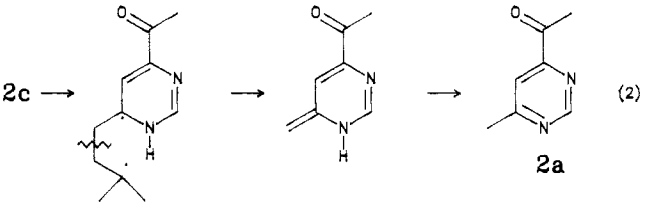
Photochemical Experiments. As expected from reports concerning **1b** and related 4-acylpyrimidines,[9] direct irradiation of **1a** in *tert*-butyl alcohol containing 5% benzene[10] with $\lambda > 340$ nm leads to **3**[11] through hydrogen abstraction by N(3) (eq 1[12]).



(1)

Alexander showed that this is a quenchable triplet reaction involving a nitrogen $n\pi^*$ state approximately isoenergetic with the carbonyl triplet.[9,13] Using as models the energies of the reactive carbonyl triplets of 2- and 4-acetylpyridine,[14] we estimate that these isoenergetic carbonyl and nitrogen triplets of **1a** have $E_T \sim 70$–71 kcal/mol. Since we found that isomerization of **1a** to **3** can be sensitized by 4-chlorobenzophenone ($E_T = 68.8$ kcal/mol in polar solvent[15]), the energy of the active triplet in **1a** cannot be much greater than this estimate. We have also observed this isomerization of **1a** to **3** on direct irradiation at shorter wavelengths ($\lambda > 200$ nm) and on triplet sensitization in acetone as solvent.

Direct irradiation of **2c** under these conditions ($\lambda > 340$ nm) or its sensitization using 1-indanone ($E_T \sim 75.7$ kcal/mol[16]) or phenone sensitizers of lower energy failed to bring about the analogous conversion of **2c** to **2a** (eq 2); reaction mixtures darkened, **2c** was destroyed very slowly, and no volatile products were recovered.[17] Formation of a triplet of **2c** under the direct conditions was confirmed by isomerization of added *cis*-piperylene to *trans*-piperylene;[18] transfer of triplet energy from typical phenone sensitizers to **2c** was demonstrated by observing that **2c** quenches valerophenone triplets following Stern–Volmer kinetics[19a] ($k_q\tau \sim 55$ M^{-1} [19b]). Taken together, these experiments establish that, as expected, conditions populating the reactive nitrogen $n\pi^*$ triplet of **1a** also populate a triplet state of **2c**, but that this state does not lead to hydrogen abstraction by N(1). In contrast, irradiation of **2c** in acetone as solvent and triplet sensitizer ($E_T \sim 79$–82 kcal/mol[20]) does result in fragmentation to **2a**[21] (eq 2).



(2)

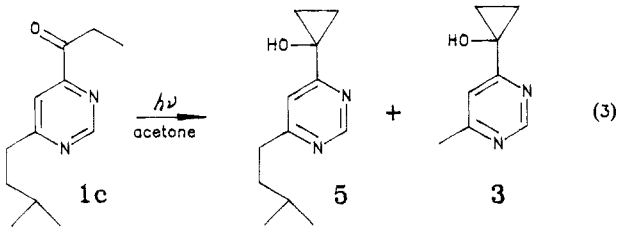
Similarly, direct irradiation of **2c** with $\lambda > 200$ nm also gives **2a**. Abstraction by N(1) in **2c**, then, is mediated by a triplet that is accessible on sensitization by acetone but not indanone; we conclude that this triplet has $E_T \sim 79$–84 kcal/mol. Presumably this upper triplet is also reached on direct irradiation with $\lambda > 200$ nm through intersystem crossing from an upper singlet. We have also determined an approximate quantum yield at low conversion for the acetone-sensitized fragmentation of **2c**, $\Phi_p \sim 0.06$. This experiment was carried out at ~313 nm (potassium chromate

(3) Hoover, R. J.; Kasha, M. *J. Am. Chem. Soc.* **1969**, *91*, 6508.
(4) See for example: (a) Turro, N. J.; Ramamurthy, V.; Cherry, W.; Farneth, W. *Chem. Rev.* **1978**, *78*, 125. Sadler, D. E.; Wendler, J.; Olbrich, G.; Schaffner, K. *J. Am. Chem. Soc.* **1984**, *106*, 2064. (b) Schuster, D. I.; Calcaterra, L. T. *Ibid.* **1982**, *104*, 6397.
(5) (a) Caronna, T.; Fronza, G.; Minisci, F.; Porta, O. *J. Chem. Soc., Perkin Trans. 2* **1972**, 2035. (b) Sakamoto, T.; Ono, T.; Sakasai, T.; Yamanaka, H. *Chem. Pharm. Bull.* **1980**, *28*, 202.
(6) Sakamoto, T.; Sakasai, T.; Yamanaka, H. *Chem. Pharm. Bull.* **1980**, *28*, 571.
(7) Price, C. C.; Pappalardo, J. A. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 186.
(8) Bredereck, H.; Gompper, R.; Morlock, G. *Chem. Ber.* **1957**, *90*, 942.
(9) Alexander, E. C.; Jackson, R. J., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 5665; **1976**, *98*, 1609. These workers used 313-nm light.
(10) This solvent mixture is used throughout unless otherwise specified.
(11) Pyrimidinylcyclopropanols were fully characterized. Spectroscopic data given in the Experimental Section are compatible with those reported (ref 9) for 1-(4-pyrimidinyl)-1-cyclopropanol.
(12) The order of steps shown is that suggested in ref 9; cyclization to a cyclopropyloxy species could conceivably precede transfer of hydrogen from nitrogen to oxygen.
(13) More specifically, Alexander (ref 9) concluded that in 4-acylpyrimidines there are either two nearly isoenergetic $n\pi^*$ triplets involving oxygen and N(3), respectively, or a single vibronically mixed triplet involving both atoms.
(14) These are 70.9 and 70.3 kcal/mol, respectively, in alcohol; in appropriate substrates these states can lead to type II cleavage: (a) Arnold, D. R. *Adv. Photochem.* **1968**, *6*, 301. (b) Wagner, P. J.; Capen, G. *Mol. Photochem.* **1969**, *1*, 178. (c) Wagner, P. J.; Leventis, N. *J. Am. Chem. Soc.* **1987**, *109*, 2188.
(15) Murov, S. L. *Handbook of Photochemistry*; Marcel Dekker: New York, 1973; p 13.
(16) Amrein, W.; Larsson, I.-M.; Schaffner, K. *Helv. Chim. Acta* **1974**, *57*, 2519. Catalani, L. H.; Wilson, T. *J. Am. Chem. Soc.* **1987**, *109*, 7458.
(17) This darkening may be analogous to the formation of colored byproducts in type II reactions of acylpyridines (ref 14b).
(18) Hammond, G. S.; Leermakers, P. A.; Turro, N. J. *J. Am. Chem. Soc.* **1961**, *83*, 2396.
(19) (a) Wagner, P. J. In *Creation and Detection of the Excited State*; Marcel Dekker: New York, 1971; Vol. 1, Part A, p 173. (b) Quenching of valerophenone triplets by 2,5-dimethyl-2,4-hexadiene under similar conditions gives $k_q\tau = 40$ M^{-1}: Wagner, P. J. *J. Am. Chem. Soc.* **1967**, *89*, 5898.
(20) Schmidt, M. W.; Lee, E. K. C. *J. Am. Chem. Soc.* **1970**, *92*, 3579 and references cited therein.
(21) Properties of **2a** were compatible with those of an authentic sample prepared as described in ref 6.

filter) and a concentration of 0.007 M substrate in acetone as solvent, with the concomitant formation of acetone from type II elimination of 2-hexanone (1.0 M in the solvent pentane) as a chemical actinometer.[22] Control experiments indicated that Φ_p is independent of concentration in the range 0.02–0.007 M, thus assuring that no acetone singlets and all acetone triplets were quenched by the substrate at the concentration employed for determination of the quantum yield.[4b,23] This control also assures that the observed reactions of these ketones in acetone result from triplet energy transfer. Alexander had found Φ_p for the isomerization of **1b** in *tert*-butyl alcohol to be ~0.34.[9]

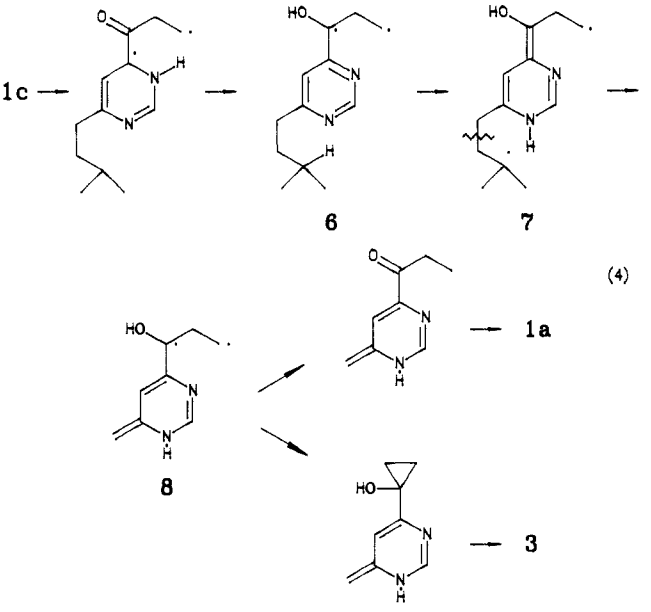
The triplet that activates abstraction in **2c** then lies ~8–14 kcal/mol above the triplet active in **1a**, and hydrogen abstraction from this state is ~15–20% as efficient as that from the lower triplet. As nitrogen $\pi\pi^*$ states are expected to be some 3 orders of magnitude less reactive in hydrogen abstraction than $n\pi^*$ states,[24] this efficiency in reaction of **2c** is consistent only with an $n\pi^*$ assignment for the upper state; it is then presumably the second nitrogen $n\pi^*$ triplet. Since the upper triplet states of pyrimidine itself have not been completely characterized[25] and are known to be closely spaced,[26] and since the substituents present in **1** and **2** should significantly perturb the ordering and energy of the triplets in these substituted pyrimidines,[3,25a] it remains uncertain whether the active state in **2c** is T_2, T_3, or some higher triplet. Its precise position depends upon its energy relative to the unknown energies of the lowest $\pi\pi^*$ states in these systems and upon the extent to which vibronic mixing reduces the number of separate states.[27]

With these results in hand we were curious about the behavior of **1c**, an acylpyrimidine whose structure permits intramolecular abstraction of hydrogen by either nitrogen atom. Interestingly, the photochemistry of **1c** provides evidence for a novel fragmentation mechanism not possible in **1a** or **2c**. On either direct or acetone-sensitized irradiation of **1c** the products were **5**,[11] **1a**, and/or **3**. Direct irradiation with $\lambda > 200$ nm furnished all three products in modest yields that were dependent on the time of reaction, but results in acetone and on direct irradiation at longer wavelengths were more informative. Thus photolysis of **1c** to ~80% conversion in acetone produces 74% of a mixture of cyclopropanols **5** (74%) and **3** (26%) (eq 3), rather than **5** and **1a**,



(3)

which are the primary products anticipated from the behavior of **1a** and **2c**. Several further experiments were necessary to clarify the origin of **3** in this reaction. A control experiment confirmed that **5** is stable to the reaction conditions and, therefore, is not the precursor of **3**. Another control employing **1a** and **1c** revealed that at least some of **1a**, had it been formed, would have survived and would not have undergone secondary photolysis to **3** in the presence of the greater concentration of **1c**. Moreover, the ratio of **5** to **3** was unchanged on approximately 4-fold variation in the intensity of incident light in irradiation of **1c**, a result establishing that an identical number of photons is necessary to form each of these products. We conclude that there is a monophotonic path from **1c** to **3**. Also, direct irradiation of **1c** at $\lambda > 340$ nm yields **5** (90%) along with small amounts of **1a** (2%) and **3** (3%). Formation of **1a** and **3** indicates that N(1) has abstracted hydrogen in this reaction, although, as shown above, the upper triplet that activates N(1) is not accessible on direct irradiation at these wavelengths. These various observations require that there be a path to **1a** and **3** that is available to **1c** but that has no counterpart in the photochemistry of **2c**. They point to a mechanism that begins with abstraction of hydrogen by N(3) and also involves abstraction by N(1) but without excited state activation of N(1). Such a mechanism is shown in eq 4. Formation



(4)

of **5** can occur as in eq 1 by way of **6**, but **6** can alternatively undergo hydrogen transfer from the isopentyl side chain to N(1), giving **7**. This then fragments to **8**, which can either close to the cyclopropanol or else transfer hydrogen from oxygen to carbon and restore the carbonyl group. Rearomatization of the resulting intermediates furnishes **3** and **1a**, respectively. Collapse of **6** to **5** should be rapid relative to attainment of a conformation of the side chain that permits formation of **7**, and this is consistent with the observation that **1a** and **3** are minor products. Also in line with experimental results, this mechanism cannot operate in **2c**, since the initial abstraction by N(3) does not occur from the shorter acetyl group at C(4).

In summary, this investigation has demonstrated that the first nitrogen triplet (E_T ~ 70–71 kcal/mol) in these pyrimidinyl ketones can mediate direct abstraction by N(3) but not N(1), that there is a nitrogen triplet some 8–14 kcal/mol higher than the first triplet that does activate direct abstraction by N(1), and that initial abstraction by N(3) apparently can lead to abstraction by N(1) in a monophotonic process.

Experimental Section

Materials and Equipment. Unless otherwise indicated, gas chromatography (GLC) was carried out on a Varian Aerograph Model 920 gas chromatograph with either (A) a 25% QF-1, 6-ft column or (B) a 10% OV-101, 6-ft, column, packed in 0.25-in. aluminum or stainless steel tubing with 45/60 Chromosorb W. Unless otherwise indicated, analytical GLC was carried out on a Varian Model 1440 temperature-pro-

(22) Coulson, D. R.; Yang, N. C. *J. Am. Chem. Soc.* **1968**, *88*, 4511. Wagner, P. J. *Tetrahedron Lett.* **1968**, 5795. Murov, S. L. *Handbook of Photochemistry*; Marcel Dekker: New York, 1973; pp 126–127.

(23) Zimmerman, H. E.; Swenton, J. S. *J. Am. Chem. Soc.* **1967**, *89*, 906. Zimmerman, H. E.; Schissel, D. N. *J. Org. Chem.* **1986**, *51*, 196.

(24) Experimental evidence: Bent, D. V.; Hayon, E.; Moorthy, P. N. *J. Am. Chem. Soc.* **1975**, *97*, 5065 and references cited therein. Theoretical calculations: Formosinho, S. J. *J. Chem. Soc., Faraday Trans. 2*, **1976**, *72*, 1332 and references cited therein.

(25) (a) Inoue, A.; Lim, E. C. *Chem. Phys. Lett.* **1979**, *62*, 250. (b) Nonhof, C. J.; van der Waals, J. H. *Ibid.* **1982**, *92*, 581, 588.

(26) In pyrimidine itself the lowest observed triplets are $^3B_1$ ($n\pi^*$), ~82 kcal/mol, and $^3A_1$ ($\pi\pi^*$), ~85 kcal/mol; there is evidence of some mixing of these states: Hochstrasser, R. M.; Marzzacco, C. *J. Chem. Phys.* **1968**, *49*, 971. Takamura, T.; Uchida, K.; Fujita, M.; Shindo, M.; Suzuki, N.; Baba, H. *Chem. Phys. Lett.* **1980**, *73*, 12 and references cited therein. Vogler, H. *Z. Naturforsch., A: Phys., Phys. Chem., Kosmophys.* **1986**, *41A*, 959. The second $n\pi^*$ state ($^3A_2$) lies above these and possibly also above the second $\pi\pi^*$ state ($^3B_2$) (ref 25). An INDO/S calculation gives an energy difference of 10.4 kcal/mol between the two lowest $n\pi^*$ triplets: Ito, H.; I'Haya, Y. *J. Bull. Chem. Soc. Jpn.* **1976**, *49*, 940. In 4-methylpyrimidine T_1 lies at ~84 kcal/mol, but there is "essentially no change in electronic structure on methyl substitution": Uchida, K.; Yamazaki, I.; Baba, H. *Chem. Phys.* **1978**, *35*, 91.

(27) In this regard see ref 13.

grammable gas chromatograph with a 2.5% QF-1, 10-ft, column packed in $^1/_8$-in. stainless steel tubing with 120–140-mesh Chromosorb W. Column chromatography was performed on silica gel (230–400 mesh) from EM Science or silica gel (70–150 mesh) from ICN Biochemicals. Preparative thin-layer chromatography (TLC) was performed on 2000-μm silica gel GF plates from Analtech. All NMR spectra were recorded on either a Varian Model T-60 (60 MHz) or a Nicolet/Oxford Model NT-300 (300 MHz) spectrometer and are reported in parts per million downfield from tetramethylsilane, which was employed as an internal standard (δ). Infrared spectra were recorded on a Perkin-Elmer Model 237B grating infrared spectrophotometer. Ultraviolet absorption spectra were recorded on a Cary 14 recording spectrophotometer. Mass spectral analyses were performed by The Rockefeller University Mass Spectrometric Biotechnology Resource on a VG-70250 magnetic sector instrument. Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are corrected. Molecular distillations were performed with a Kugelrohr apparatus at reduced pressure. Organic solutions obtained by workup of reaction mixtures were dried by washing with brine prior to treatment with anhydrous sodium or magnesium sulfate.

Preparation of 4-(3-Methylbutyl)pyrimidine. A solution of formamide (63 mL, 1.6 mol) and 1-chloro-6-methyl-1-hepten-3-one[7] (12.8 g, 0.08 mol) was heated at 160 °C for 6 h.[8] The darkened solution was cooled and poured into a 15% aqueous sodium hydroxide solution which had been previously cooled in an ice bath. The two layers which resulted were separated. The aqueous layer was extracted three times with ether. All organic phases were combined, washed twice with brine, dried, and concentrated *in vacuo* to provide 9.2 g of a brown oil. Purification by molecular distillation (90–108 °C at 6–8 mmHg) yielded 2.3 g (20%) of a clear liquid: ^{1}H NMR ($CDCl_3$) δ 9.1 (s, 1 H), 8.6 (d, 1 H), 7.2 (dd, 1 H), 2.7 (t, 2 H), 1.4–1.9 (m, 2 H), 0.9 (d, 3 H); IR (CCl_4) 2975, 2950, 2875, 1580, 1550, 1475, 1390, 1370, 995, 830 cm^{-1}. Anal. ($C_9H_{14}N_2$) C, H, N.

Preparation of 4-Acyl-6-(3-methylbutyl)pyrimidines (1c and 2c). To an aqueous solution (30 mL) of 4-(3-methylbutyl)pyrimidine (1.5 g, 0.01 mol) containing silver nitrate (16.9 mg, 0.001 mol), pyruvic acid (2.2 g, 0.025 mol) (for **2c**) or 2-ketobutyric acid (2.0 g, 0.02 mol) (for **1c**), and concentrated sulfuric acid (0.05 mol) was slowly added an aqueous solution (40 mL) of ammonium peroxysulfate (4.5 g, 0.02 mol) with stirring at 50 °C.[5b] The reaction mixture was stirred at this temperature for 1.5 h and then cooled and extracted thrice with ether. The ethereal layers were combined, dried, and concentrated in vacuo to provide viscous golden oils. Purification was accomplished by preparative GLC on column A, resulting in **1c** or **2c** as pale yellow oils in 40–60% yield. For **2c**: ^{1}H NMR ($CDCl_3$) δ 9.23 (s, 1 H), 7.75 (s, 1 H), 2.88 (t, 2 H), 2.78 (s, 3 H), 1.64 (m, 3 H), 0.95 (d, 6 H); ^{13}C NMR ($CDCl_3$) δ 199.84 (s), 173.63 (s), 158.58 (d), 158.43 (s), 115.97 (d), 37.85 (t), 36.08 (t), 27.85 (s), 25.71 (d), 22.35 (q); IR (neat) 2950 (m), 1710 (s), 1590 (s), 1520 (m), 1380 (m) cm^{-1}; UV (CH_3OH) 266 nm (2600); MS, *m/z* 192.1263 (M^+, calcd for $C_{11}H_{16}NO$ 192.1263). For **1c**: ^{1}H NMR ($CDCl_3$) δ 9.22 (d, 1 H), 7.58 (d, 1 H), 3.2 (q, 2 H), 2.97 (t, 2 H), 1.65 (m, 3 H), 1.24 (t, 3 H), 0.97 (d, 6 H); ^{13}C NMR ($CDCl_3$) δ 202.13 (s), 173.43 (s), 158.99 (d), 158.27 (s), 115.95 (d), 37.74 (t), 35.96 (t), 31.20 (t), 27.74 (d), 22.24 (q), 7.48 (q); IR ($CHCl_3$) 3000 (s), 1705 (s), 1580 (s), 1375 (m) cm^{-1}; UV (CH_3OH) 266.5 nm (2600); MS, *m/z* 206.1419 (M^+, calcd for $C_{12}H_{18}N_2O$ 206.1419).

Preparation of 6-Methyl-4-(1-oxopropyl)pyrimidine (1a). A procedure analogous to the above for preparation of **1c** was employed, starting with commercially available 4-methylpyrimidine. Preparative GLC purification on column A yielded **1a** as a white crystalline material: mp 41–42 °C; ^{1}H NMR ($CDCl_3$) δ 9.20 (d, 1 H), 7.75 (d, 1 H), 3.20 (q, 2 H), 2.63 (s, 3 H), 1.22 (t, 2 H); ^{13}C NMR ($CDCl_3$) δ 202.28 (s), 169.39 (s), 158.50 (d), 158.34 (s), 116.80 (d), 31.34 (q), 24.45 (t), 7.59 (q); IR ($CHCl_3$) 2960 (m), 1715 (s), 1580 (s), 1375 (m) cm^{-1}; UV (CH_3OH) 265 nm (2800); MS, *m/z* 150.0793 (M^+, calcd for $C_8H_{10}N_2O$ 150.0793).

General Procedure for Photolyses. Solutions of pure 6-alkyl-4-acylpyrimidines (0.001–0.01 M) in 5:95 benzene *tert*-butyl alcohol (v/v) as solvent, unless indicated otherwise, contained in a toroidal Pyrex glass vessel, were irradiated under a N_2 atmosphere with a Hanovia 450-W medium-pressure mercury-arc lamp employing glass filter sleeves for selection of desired wavelength range. Filters used were Vycor (λ >200 nm), Pyrex (λ >280 nm), and uranium glass (λ >340 nm). Acetone-sensitized irradiations were conducted employing acetone as solvent. Reaction progress was followed by GLC analysis, the solvent was removed by concentrating in vacuo, and the residues were purified by column or thin-layer chromatography or preparative GLC.

Direct Photolyses of 1a. A. Vycor-filtered irradiation of **1a** (0.01 M) led to its conversion into 1-(6-methylpyrimidin-4-yl)cyclopropanol (**3**) (98%): ^{1}H NMR ($CDCl_3$) δ 8.88 (d, 1 H), 7.45 (d, 1 H), 4.93 (br s, 1 H), 2.53 (s, 3 H), 1.41 (s, 4 H); ^{13}C NMR ($CDCl_3$) δ 172.91 (s), 166.19 (s), 157.25 (d), 115.85 (d), 56.50 (s), 23.89 (q), 19.99 (t); IR ($CHCl_3$) 3560 (m), 3300 (m, broad), 3010 (s), 1610 (s), 1330 (m), 1295 (m), 1250 (m) cm^{-1}; MS, *m/z* 150.0793 (M^+, calcd for $C_8H_{10}N_2O$ 150.0793).

B. Pyrex-filtered irradiation of **1a** (99 mg, 0.01 M) for 22 h followed by GLC purification (column A, 120 °C) yielded 34 mg of **1a** and 65 mg (66%) of **3**.

C. Uranium glass-filtered irradiation of **1a** (73 mg, 0.01 M) led to formation of **3** (90%) as analyzed by GLC.

Direct Photolyses of 1c. A. Vycor-filtered irradiation of **1c** (37 mg, 0.01 M) for 1 h resulted in 15% recovery of **1c** along with three products in isolated yields as indicated: **1a** (23%), **3** (11%), and **5** (29%). For **5**: ^{1}H NMR ($CDCl_3$) δ 8.93 (d, 1 H), 7.21 (d, 1 H), 2.77 (t, 2 H), 1.61 (m, 2 H), 1.39 (s, 4 H), 1.3 (m, 1 H), 0.96 (d, 6 H); ^{13}C NMR ($CDCl_3$) δ 171.08 (s), 170.83 (s), 157.57 (d), 113.941 (d), 57.06 (s), 38.05 (t), 35.96 (t), 27.91 (d), 22.40 (q), 19.87 (t); IR ($CHCl_3$) 3600 (s), 3450 (br), 2970 (s), 1600 (s), 1380 (m) cm^{-1}; MS, *m/z* 206.1419 (M^+, calcd for $C_{12}H_{18}N_2O$ 206.1304).

B. Uranium-glass filtered irradiation of **1c** (0.01 M) for 3 h led to ~50% conversion to three products in the estimated yields indicated: **1a** (2%), **3** (3%), and **5** (90%).

Direct Photolyses of 2c. A. Vycor-filtered irradiation of **2c** (0.01 M) for 30 min, led to a 32% recovery of **2c** and formation of **2a**[21] (22%) as analyzed by GLC.

B. Uranium-filtered irradiation of **2c** (0.01 M) resulted in very slow destruction of **2c** and no volatile products.

Acetone-Sensitized Photolysis of 2c. An acetone solution 0.001 M in **2c** (100 mg, 5.2×10^{-4} mol) was irradiated for 1 h through Pyrex. After evaporation of the solvent, the residue (177 mg) was subjected to column chromatography (silica, $CHCl_3$–CH_3OH gradient) to provide 33 mg of **2a**[21] (46%) as white needles.

Acetone-Sensitized Photolysis of 1a. An acetone solution of **1a** (48 mg, 3.2×10^{-4} mol) was irradiated through Pyrex for 2 h. Evaporation of the solvent left 205 mg of residue which was purified by preparative TLC (5% CH_3OH/95% $CHCl_3$) to yield 45 mg of **3** (93%).

Acetone-Sensitized Photolysis of 1c. An acetone solution 0.001 M in **1c** (100 mg, 4.8×10^{-4} mol) was irradiated for 5.5 h through Pyrex. Evaporation of the solvent left 372 mg of residue which was purified by preparative TLC (95% $CHCl_3$/5% CH_3OH) to provide 20 mg of recovered **1c**, 55 mg (55%) of **5**, and 14 mg (19%) of **3**. Essentially the same ratio of **5** to **3** was formed on photolysis of a sample of **1c** held at approximately twice the distance from the light source (see control experiment D).

Isomerization of *cis*-Piperylene by 2c. Solutions of **2** (0.025 M) containing concentrations of isomerically pure *cis*-piperylene (0.28–25 mM) were irradiated through uranium glass for 1 h. GLC analysis (X5-1150 column, 20 ft, room temperature) revealed a linear increase in formation of *trans*-piperylene with increasing concentrations of starting *cis*-piperylene.

Quenching of Valerophenone Triplets by 2c. Solutions of valerophenone (0.2 M) containing concentrations of **2c** (0.1–0.4 M) were irradiated through uranium glass for 1.5 h and analyzed by GLC (10% OV101, 10 ft, 110 °C); a Stern–Volmer plot of the data[19] gave slope = 55 M^{-1}, *y* intercept = 9, r^2 factor = 0.999.

Control Experiments. A. Cyclopropanol **5** was recovered unchanged from irradiation under the following conditions: (1) through uranium glass, 5 h, 0.01 M solution; (2) through Vycor, 1.25 h, 0.01 M solution; (3) acetone solvent, through Pyrex, 2 h, 0.001 M.

B. Ketone **2a** (0.001 M) was recovered unchanged from irradiation in acetone solution through Pyrex for 3 h.

C. An acetone solution containing **1c** (1.0 mM) and **1a** (0.05 mM) was irradiated through Pyrex for 30 min. GLC analysis indicated that **1a** is not destroyed under these conditions.

D. Pyrex tubes containing **1c** (0.001 M) in acetone were irradiated simultaneously for 1 h in a merry-go-round apparatus at distances of 3.40 and 6.58 cm from the light source. Analysis indicated product distribution and relative yields were identical at the two distances. The ratio of light intensities was 3.74.

Quantum Yield Studies. The quantum yield for product formation in acetone-sensitized irradiation of **2c** was determined with the type II reaction of 2-hexanone[22] as an actinometer. Acetone solutions 0.007 M in **2c**, along with pentane solutions 1.0 M in 2-hexanone, both in duplicate, were irradiated through a potassium chromate filter solution in a merry-go-round apparatus employing a Hanovia 450-W lamp for 16.82 h. GLC analysis (HP 3390A integrator) with 4-chlorobenzophenone as a standard provided peak areas for calculation of the quantum yield. This yielded $\Phi_p \sim 0.06$ at ~5% conversion. Control experiments involving 2.5 h irradiation of 0.02, 0.01, and 0.007 M solutions of **1a** in acetone showed no variation in Φ_p as a function of concentration.

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Fast Hydrolysis of an Aliphatic Amide at Neutral pH and Ambient Temperature. A Peptidase Model

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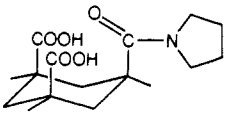
Abstract: An intramolecular-catalyzed cleavage of an aliphatic amide under biological conditions (ambient temperature, neutral pH, absence of alien transition metals) was found to occur with the fastest rate yet recorded for such a reaction: $t_{1/2}$ = 8 min (pD = 7.05, 21.5 °C) and an effective molarity EM > 10^{14} M. The peptidase "model" has a carboxyl oxygen perched above the plane of the amide carbonyl at a van der Waals contact distance of 2.8 Å. The carboxyl is poised for synchronous nucleophilic attack and proton delivery. Evidence (based on the observation that the amide actually cleaves much faster than the corresponding methyl ester) suggests that proton transfer plays a key role in the rate-determining step. The results show that an enzyme need not employ esoteric mechanisms to cleave an unreactive entity such as an amide. If the enzyme merely positions a carboxyl adjacent to an amide substrate with the geometry established in the "model", most of the necessary catalytic power would be achieved.

Human beings admire speed whether it be animal, mechanical, or chemical in origin. Within the chemistry arena, fast reactions signify milder conditions and reduced energy consumption. But the desire to achieve speed is motivated by more than economics. Chemists are challenged by a rival, the enzyme, that outpaces us with a perplexing regularity. α-Chymotrypsin, for example, hydrolyzes amides rapidly at neutral pH and ambient temperature.[1] In contrast, a typical chemical procedure for hydrolyzing amides[2] calls for a 10-h reflux in 8 N HCl. Although "models" attempting to duplicate α-chymotrypsin-like rates have been successful with *p*-nitrophenyl esters, rate enhancements often vanish when less reactive ("natural") carboxylic acid derivatives are employed.[3] In the present article we describe cleavage of an aliphatic amide I under biological conditions free from transition metals. Neither a substituent (such as a *p*-nitrophenyl group on the nitrogen) nor ring-strain (as in a β-lactam) nor amide-twisting (as in a bridgehead amide) artificially activate the substrate. To our knowledge, the reaction constitutes the fastest peptidase "model" at pH 7 on record.[4-9]



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Experimental Section

General Procedures. Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 983 IR spectrophotometer. ^{1}H NMR spectra were obtained with a General Electric QE-300 spectrometer. NMR data are reported as follows: chemical shift (δ) downfield from internal tetramethylsilane, multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet; br s, broad signal), coupling constant (Hz), integration, and assignment. Precise mass was determined with the aid of a VG Analytical MM 7070S high-resolution mass spectrometer.

Anhydride Acid III. The precursor *cis,cis*-1,3,5-trimethylcyclohexane-1,3,5-tricarboxylic acid[10] was prepared following the published procedure.[11] It was sublimed at 190–195 °C (0.20 mm) to give white crystals of the corresponding anhydride acid III, mp 205–208 °C, in 85% yield. IR (KBr): 1796, 1766, 1702, 1001 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.72 (d, J = 14.1 Hz, 2 H, equat CH), 2.05 (d, J = 13.8 Hz, 1 H, equat CH), 1.35 (s, 9 H, Me), 1.30–1.50 (m, 3 H, axial CH).

Anhydride Acid Chloride. A suspension of anhydride acid III (414 mg; 1.72 mmol) in dry benzene (18 mL) was cooled to 0 °C and oxalyl chloride (2.2 mL; 25.2 mmol) was added followed by 1 drop on *N,N*-dimethylformamide. The resulting mixture was stirred at room temperature for 16 h. The residue obtained upon evaporation of solvent was recrystallized from dry dichloromethane to give 355 mg (80%) of anhydride acid chloride as pale-yellow crystals; mp 253–255 °C (lit.[10] mp 255–260 °C). IR (KBr): 1793, 1770, 1005 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.80 (d, J = 13.8 Hz, 2 H, equat CH), 2.04 (d, J = 13.5 Hz, 1 H, equat CH), 1.39 (d, 1 H, axial CH), 1.35 (s, 3 H, Me–C–COCl), 1.34 (s, 6 H, Me–C–COO), 1.30–1.40 (2 H, axial CH).

Anhydride Amide II. A solution of anhydride acid chloride (300 mg; 1.16 mmol) in dry acetonitrile (40 mL) was purged with nitrogen, and dry pyridine (3.0 mL; 37 mmol) was added by means of a syringe. This mixture was cooled to −40 °C and pyrrolidine (101 μL; 1.21 mmol) was added, resulting in the immediate development of an intense yellow color. The homogeneous mixture was stirred at room temperature for 3 h. Evaporation of solvent gave 495 mg of yellow crystals which were flash-chromatographed on 7 g of aluminum oxide, using dichloromethane as eluent, to yield 214 mg (63%) of anhydride amide as white crystals; mp 215–217 °C. Precise mass for $C_{16}H_{23}NO_4$: 293.1627 (calcd), 293.1623 (found). IR (KBr): 1790, 1760, 1611, 1008 cm^{-1}. ^{1}H NMR (CDCl3) δ 3.46 (t, J = 6.6 Hz, 4 H, N–CH_2), 2.91 (d, J = 13.5 Hz, 2 H, equat CH), 2.00 (d, J = 13.5 Hz, 1 H, equat CH), 1.87 (br s, 2 H, N–CH_2–CH_2), 1.77 (br s, 2 H, N–CH_2–CH_2), 1.35 (d, 1 H, axial CH), 1.34 (s, 6 H, Me–C–COO), 1.22 (s, 3 H, Me–C–CON), 1.16 (d, J = 13.5 Hz, 1 H, axial CH).

Kinetic Measurements. Rate of anhydride opening in anhydride amide II (k_1 in eq 1) was studied between pD 2 and 11. In a typial experiment,

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