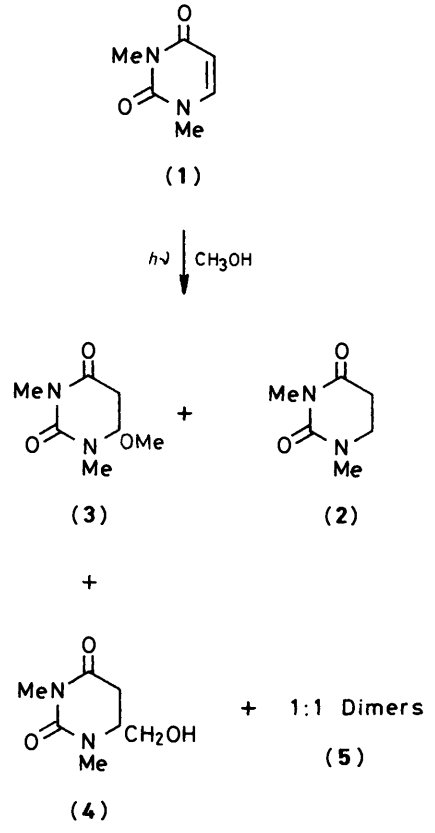
Photochemistry of 1,3-Dimethyluracil. A Novel Photochemical Reaction Leading to 3,5-Dialkoxycarbonyl-1,2-and -1,4-Dihydropyridines

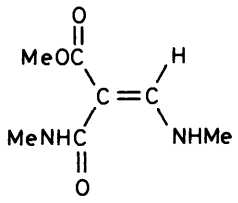
Marianne Kristiansen, Jens Eriksen,*† and Karl Anker Jørgensen*
Department of Chemistry, Aarhus University, DK-8000 Aarhus C, Denmark

A new photochemical reaction of 1,3-dimethyluracil is reported. Irradiation of 1,3-dimethyluracil in methanol leads to a fluorescent mixture of 1,4-dihydro- and 1,2-dihydro-3,5-dimethoxycarbonyl-1-methylpyridines. Results from photolysis in other alcoholic solvents are also reported.

The photochemistry of 1,3-dimethyluracil (DMU) (**1**) in alcoholic solution is of great interest as a model system for the interaction of the nucleoside uracil with the hydroxy groups of surrounding amino acids on exposure to u.v. light.[1] The photolysis of DMU in methanol has been known for some time and the various photoproducts (**2**)—(**5**) have been



detected under various irradiation conditions,[2,3] but we have found that the product distribution is very sensitive to the wavelength utilized.[4] From these studies of DMU in methanol we were also able to identify a new product, methyl 3-methylamino-2-(*N*-methylcarbamoyl)propenoate (**6**), in about 10% yield.[4] It has been suggested that (**6**) was formed by a Woodward–Hoffmann allowed disrotatory electrocyclic ring closure in the photochemical step *via* a Dewar pyrimidine ion as intermediate.[4] A similar type of intermediate has also been



(**6**) (*E* or *Z*)

observed in the photochemistry of pyrimidin-4-ones in aqueous solution.[5]

From this photolytic route, as well as from an independent route leading to (**6**), was also isolated a fluorescing material with an emission maximum in acetonitrile at 450 nm and an excitation maximum at 390 nm. We have now been able to identify two new products and report here the formation of these photoproducts in different alcoholic solvents and also the formation of enamines similar to (**6**) in solvents other than methanol.

Results and Discussion

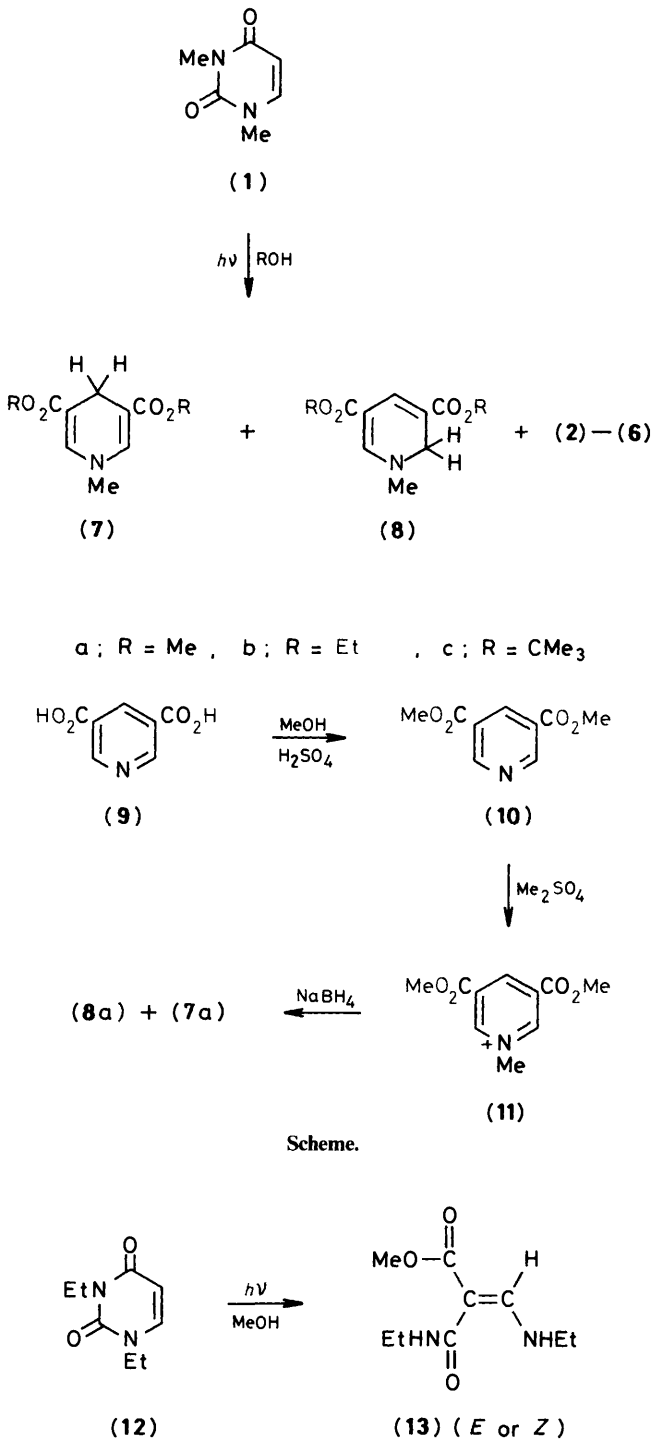
In addition to the previous photoproducts (**2**)—(**6**), irradiation of DMU in ethanol using a Rayonet reactor at 254 nm or an unfiltered Hanovia lamp leads the formation of 1,4-dihydro-3,5-dimethoxycarbonyl-1-methylpyridine (**7a**) and 1,2-dihydro-3,5-dimethoxycarbonyl-1-methylpyridine (**8a**) (see Experimental for details).

Both products exhibited strong blue fluorescence with emission and excitation maxima as mentioned above. The identification of (**7a**) and (**8a**) was based upon spectral data and was confirmed by an independent synthesis as outlined in the Scheme. The highest yield of (**7a**) and (**8a**) (1—2%) was obtained by photolysis of DMU in methanol in quartz glassware using an unfiltered Hanovia lamp and dichloroethylene as a triplet quencher which suppressed the formation of products (**2**)—(**5**). Photolysis of DMU in ethanol, propan-2-ol and 2-methylpropan-2-ol also gave fluroescent products. With ethanol or 2-methylpropan-2-ol as solvent, it was possible to separate two products in low yields (<1%), which have been identified as the analogous 1,4-dihydropyridines (**7b, c**) and 1,2-dihydropyridines (**8b, c**), respectively. The yield of fluorescent material in propan-2-ol solution was so low that an identification was not possible.

Photolysis of 1,3-diethyluracil (DEU) (**12**) in methanol led to several products, one of which was isolated and identified as methyl 3-ethylamino-2-(*N*-ethylcarbamoyl)propenoate (**13**) in agreement with the mechanism we had previously proposed for the formation of (**6**).[4]

Besides the enamine (**13**) a fluorescent product was also

† *Present address:* Department of Chemistry, Sultan Qaboos University, P.O. Box 32486 Al Khod, Sultanate of Oman.



Scheme.

obtained in very low yield. A g.c.-m.s. showed peaks corresponding to the 1,4-dihydro- and/or 1,2-dihydro-1-ethyl-3,5-dimethoxycarbonylpyridine, but further identification was not possible.

The mechanism for the formation of dihydropyridines from DMU or DEU in alcohols is not obvious to us. We have investigated the photochemistry of two likely precursors, (**6**) and (**11**). The reason for suggesting (**6**) as a potential precursor is the formation of some fluorescent material during an independent synthesis of (**6**).[4] Direct photolysis of (**6**), however, did not give any detectable amount of the dihydropyrdines. Thus, if (**6**) is involved in some way as a precursor for (**7a**) and (**8a**) it must be in combination with DMU or some intermediate formed during the photolysis of DMU. These possibilities have not been fully explored.

Van Berger and Kellogg[6] have investigated the photochemistry of (**11**) in methanol. In addition to several unidentified products, the 1,4-dihydropyridine derivative was formed in 18% yield. In our hands irradiation of (**11**) in methanol gave a variety of products, none in very high yield. Compounds such as (**7a**) and (**8a**) could at most have been present in very minor amounts indicating that (**11**) is an unlikely precursor for our dihydropyridines.

Experimental

^{1}H N.m.r. spectra were recorded on four Varian instruments: 60 MHz EM-360, 80 MHz CFT-20, 300 MHz XL-300, and 200 MHz Gemini 200. ^{13}C and DEPT spectra were recorded on the XL-300, or Gemini spectrometers. Deuteriochloroform was used as solvent and reported δ-values are relative to tetramethylsilane (TMS). I.r. spectra were recorded on a Nicolet Analytical Instruments MXS spectrometer. U.v. spectra were recorded on a Varian Cary 219 or a Kontron Uvicon 860 spectrometer. Fluorescence spectra were recorded on an Amico SPF-500 spectroflurometer. Mass spectra were recorded on a Micromass 7070F mass spectrometer. Analytical gas-liquid chromatography (g.l.c.) analyses were carried out on Hewlett–Packard 5890A gas chromatograph equipped with a model 7673A Autoinjector and a 3392A Integrator or a Hewlett–Packard model 5790 instrument. Three columns were used: a packed column Apiezon L + 1% PEG 20 M operated isothermally at 185 °C, a methylsilicone capillary column with temperature programming (100 °C for 2 min, then 4 °C/min to 140 °C), and an OV-17 capillary column with temperature programming (140 °C for 5 min, then 8 °C/min till 220 °C). Irradiations were carried out in quartz tubes of 1 cm i.d. either in a Rayonet model RPR-204 photochemical reactor or in merry-go-round surrounding a 450W Hanovia lamp. Solution of about 10^{-2}M were purged with nitrogen for 10 min prior to photolysis. Usually each sample was irradiated for 24 hrs. The solutions were then concentrated and added into a silica gel column and eluted using a solvent mixture of light petroleum (b.p. 60—80 °C) propan-2-ol, and methanol (75:4:2).

Materials. DMF (Fluka AG) was used as received. G.l.c. analysis did not show any detectable impurities; in particular, none of the compounds (**2**)—(**8**) were present. Methanol (Merck–Licrosolv), ethanol, propan-2-ol (Merck-p.a.), and 2-methylpropan-2-ol (Fluka puriss p.a.) were used as received.

Compound (**7a**): δ_H 3.00 (s, 3 H, NCH_3), 3.14 (s, 2 H, CH_2), 3.64 (s, 6 H, OCH_3), and 6.7 (s, 2 H, vinyl-H); δ_C 21.36 (CH_2), 41.07 (NCH_3), 51.31 (OCH_3), 104.30 (CH=*C*), 139.68 (H*C*=C), and 167.74 (C=O); *m/z* 211 ($M^+ - 1$), 196, 180, 152; ν_{max} 3 430, 1 700, and 1 600 cm^{-1}; λ_{max} 388, 254, and 233 nm.

Compound (**7b**): δ_H 1.20 (t, 6 H, CH_3), 3.01 (s, 3 H, NCH_3), 3.16 (s, 2 H, CH_2), 4.10 (q, 4 H, CH_2), 6.85 (s, 2 H, vinyl-H); *m/z* 239 ($M^+ - 1$), 210, 194, 182, 166, 152, and 128; λ_{max} 384, 253, and 244 nm.

Compound (**7c**): δ_H 1.26 (s, 18 H, CH_3), 3.11 (s, 3 H, NCH_3), 3.22 (s, 2 H, CH_2), and 6.92 (s, 2 H, vinyl-H); *m/z* 295 ($M^+ - 1$), 238, 220, 182, and 164.

Compound (**8a**): δ_H 2.98 (s, 3 H, NCH_3), 3.71 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3), 4.30 (s, 2 H, CH_2), 7.45 (d, *J* 1.5 Hz, vinyl-H), and 7.54 (d, *J* 1.5 Hz, 1 H, vinyl-H); *m/z* as for (**7a**).

Compound (**8b**): δ_H 1.23 (t, 3 H, CH_3), 1.25 (t, 3 H, CH_3), 2.96 (s, 3 H, OCH_3), 4.14 (q, 2 H, CH_2), 4.16 (q, 2 H, CH_2), 4.25 (s, 2 H, CH_2), 7.42 (s, 1 H, vinyl-H), and 7.49 (s, 1 H, vinyl-H); *m/z* as for (**7b**).

Preparation of (**10**).[7]—Compound (**9**) (1.0 g) was dissolved in MeOH (7.5 ml), concentrated H_2SO_4 (50 ml) was added drop-

wise and the solution was stirred for 6 h at 80 °C. The solution was neutralized with K_2CO_3 and (**10**) was extracted into diethyl ether, yield 64%; δ_H 3.90 (s, 6 H, OCH_3), 8.79 (s, 1 H, CH), and 9.29 (s, 2 H, CH).

Preparation of (**11**).[8]—Compound (**10**) (1.0 g) was dissolved in benzene (5 ml), Me_2SO_4 (2.9 ml) was added, and the solution was stirred under reflux for 3 h. Addition of acetone to the reaction mixture upon cooling led to precipitation of (**11**) as white crystals, m.p. 86—88 °C, yield 59%; δ_H 4.00 (s, 6 H, OCH_3), 4.70 (s, 3 H, NCH_3), 9.27 (s, 1 H, CH), and 9.60 (s, 2 H, CH).

Compound (**12**) was synthesized using the procedure of Ogilvie *et al.*[9] To uracil (1.0 g) dissolved in THF (90 ml) and TBAOH (58 ml) was added diethyl sulphate (5.8 ml). The solution was allowed to stand at room temperature with stirring for 16 h, isolated yield 58%; δ_H 1.19 (t, 3 H, CH_3), 1.33 (t, 3 H, CH_3), 3.78 (q, 2 H, CH_2), 3.95 (q, 2 H, CH_2), 5.60 (d, 1 H, *C*H=), and 7.15 (d, 1 H, *C*H=); *m/z* 168 (M^+), 153, 140, 124, and 112; λ_{max} 265 nm.

Compound (**13**): Yield 10%; δ_H 1.12 (s, 3 H, CH_3), 1.17 (s, 3 H, CH_3), 3.17 (q, 2 H, CH_2), 3.32 (q, 2 H, CH_2CH_3), 7.9 (d, 1 H, CH=C), 8.62 and 10.27 (both br, 1 H each, NH); *m/z* 200 (M^+) 156, 126, and 98.

Acknowledgements

Thanks are expressed to Dr. Hans Jørgen Jakobsen for recording and help with the n.m.r. spectra.

References

1 See *e.g.* (*a*) S. Y. Wang (Ed.), 'Photochemistry and Photobiology of Nucleic Acids,' Vol. I, Academic Press, New York, 1976; (*b*) M. D. Shetlar, *Photochem. Photobiol. Rev.*, 1980, **5**, 105.
2 M. D. Shetlar, *Photochem. Photobiol.*, 1976, **24**, 163.
3 (*a*) A. M. More and C. H. Thomsen, *Can. J. Chem.*, 1957, **24**, 163; (*b*) S. Y. Wang, *Nature*, 1961, **190**, 690; (*c*) J.-L. Fourrey and P. Jouin, *Tetrahedron Lett.*, 1977, 3397.
4 M. Arys, T. B. Christensen, and J. Eriksen, *Tetrahedron Lett.*, 1984, **25**, 1521.
5 (*a*) S. Hirokami, T. Takahashi, M. Nagata, Y. Hirai, and T. Yamazaki, *J. Org. Chem.*, 1981, **46**, 1769; (*b*) T. Takahashi, S. Hirokami, M. Nagata, and T. Yamazaki, *Tetrahedron Lett.*, 1985, **26**, 3247.
6 T. J. van Berger and R. M. Kellogg, *J. Am. Chem. Soc.*, 1972, **94**, 8451.
7 G. R. Hays, R. Huis, B. Coleman, D. Clague, J. W. Verhoeren, and F. Rob, *J. Am. Chem. Soc.*, 1881, **103**, 5140.
8 M. L. Peterson, *J. Org. Chem.*, 1960, **25**, 565.
9 K. K. Ogilvie, S. L. Beaucage, M. F. Gillen, and D. W. Eintwistle, *Nucleic Acids Res.*, 1979, **6**, 2261.

Received 6th March 1989; *Paper* 9/00965E