red color characteristic of tertiary phosphines[17] but decolorizes iodine instantly[18].

If the solvent for recrystallization is methanol, the outcome depends on the severity of the treatment. When the phosphonium salt 1 (10.00 g) was gently warmed with methanol (50 mL) until the solid just dissolved and the solution was cooled rapidly and filtered, part of 1 (3.20 g, 32.0%) was recovered unchanged (mp, IR). The filtrate, concentrated to half its volume, yielded 0.16 g (5.2%) of **2**. When 1 (3.00 g) was recrystallized from hot methanol (25 mL) as described above for ethanol, the first product to separate was **2** (0.15 g, 16.4%), none of 1 being recovered. When a solution of 1 in methanol was heated for 30 min at reflux prior to workup, neither substance could be isolated from the gummy mass that resulted.

B. From 3. The tertiary phosphine **3** (2.000 g, 5.15 mmol)[3] was heated in ethanol (50 mL) at reflux for 4 h under nitrogen. At first the **3** dissolved, but within 30 min white solids started to separate and were removed from time to time as the reaction proceeded, giving fractions of mp 95–97 °C dec (0.200 g), 128–148 °C (0.114 g), and 160–163 °C (0.058 g). The third fraction was identified (IR, NMR) as **2** (7.5%). The residue was a pale yellow oil: 1.260 g; n^{20}_D 1.6387; IR (neat) 3400 (vs, NH) cm^{-1}.

Pure **2**, free of solid by-products, was obtained in 2.1% yield by stirring a slurry of **3** (0.500 g, 1.29 mmol) in ethanol (20 mL) in a stoppered flask for 16 h at 25 °C. The yield of **2** was improved to 17.2% when the reaction was carried out in the presence of 0.039 g (1.29 mmol) of dissolved paraformaldehyde in an abortive attempt to prepare the methylene-bridged derivative **4**.

Acknowledgments. We thank Mr. Gordon J. Boudreaux and Mr. James B. Stanley, both of this Center, for the NMR and mass spectra.

Registry No.—**1**, 34885-67-1; **2**, 63731-20-4; **3**, 34885-71-7; ethanol, 64-17-5.

Supplementary Material Available: The ABX_2 analysis (5 pages). Ordering information is given on any current masthead page.

References and Notes

(1) One of the facilities of the Southern Region, Agricultural Research Service, U.S. Department of Agriculture.
(2) J. W. Lyons, "The Chemistry and Uses of Fire Retardants", Wiley-Interscience, New York, N.Y., 1970, p 189.
(3) A. W. Frank and G. L. Drake, Jr., *J. Org. Chem.*, **37**, 2752 (1972).
(4) E. Schumacher and R. Taubenest, *Helv. Chim. Acta*, **49**, 1439 (1966).
(5) R. Colton and Q. N. Porter, *Aust. J. Chem.*, **21**, 2215 (1968).
(6) Calcd for $C_{16}H_{18}N_2$: (P + 1)/P, 18.34. Found: 18. Calcd ratio taken from R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds", 2nd ed, Wiley, New York, N.Y., 1967, p 58.
(7) R. A. Hoffman, S. Forsen, and B. Gestblom, "NMR: Basic Principles and Progress", Vol. 5, P. Diehl, E. Fluck, and R. Kosfeld, Ed., Springer-Verlag, New York, N.Y., 1971, p 79–87.
(8) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy", Vol. 1, Pergamon Press, Oxford, England, 1965, p 388–391.
(9) E. G. Finer and R. K. Harris, *Mol. Phys.*, **12**, 457 (1967); **13**, 65 (1967).
(10) R. Schmutzler, *Inorg. Chem.*, **3**, 421 (1964).
(11) C. H. Bushweller, M. Z. Lourandos, and J. A. Brunelle, *J. Am. Chem. Soc.*, **96**, 1591 (1974).
(12) E. L. Eliel, "Stereochemistry of Carbon Compounds", McGraw-Hill, New York, N.Y., 1962, p 273.
(13) N. V. Riggs, *Aust. J. Chem.*, **16**, 521 (1963).
(14) But large deviations from equality cannot be tolerated, for they do alter the *C* and *D* parameters. This can be verified by setting $J_{AP} = J_{AX} + x$ and $J_{BP} = J_{BX} - x$ in the equations for the transition energies of the ABPX system (ref 19).
(15) C. Eberhardt and A. Welter, *Ber.*, **27**, 1804 (1894).
(16) The naming of firms or their products in this paper does not imply their endorsement by the U.S. Department of Agriculture.
(17) G. M. Kosolapoff, "Organophosphorus Compounds", Wiley, New York, N.Y., 1950, pp 25 and 26.
(18) Reference 3, footnote 42.
(19) J. Lee and L. H. Sutcliffe, *Trans. Faraday Soc.*, **54**, 308 (1958).
(20) A. D. Cohen and N. Sheppard, *Proc. R. Soc. London, Ser. A*, **252**, 488 (1959).
(21) F. S. Mortimer, *J. Mol. Spectrosc.*, **3**, 335 (1959).
(22) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed, Pergamon Press, Oxford, England, 1969, p 275.
(23) The shape of the X line spectrum changes if the ^{31}P NMR spectrum is recorded at a different field strength, as is the practice. At 24.3 MHz, the central lines (lines 17 and 18) overlap.

Photosensitized Dimerization of Methylcytosine Derivatives

Hiroyasu Taguchi, Bo-Sup Hahn, and Shih Y. Wang*

Division of Radiation Chemistry, Department of Biochemistry, School of Hygiene and Public Health, The Johns Hopkins University, Baltimore, Maryland 21205

Received June 3, 1977

Irradiation of cytosine and its 1-methyl, 4-methyl, 1,4-dimethyl, 4,4-dimethyl, and 1,4,4-trimethyl derivatives in acetone or acetone–water solutions with 313-nm light produces the corresponding derivatives of cyclobutyldicytosine (cytosine dimer, Cyt<>Cyt) with yields ranging from 14 to 86%. Under mild acid conditions, Cyt<>Cyt derivatives can be converted to the corresponding isomers of uracil dimer (Ura<>Ura) by deamination. This allows the stereoconfigurations of various Cyt<>Cyt to be determined by comparing with the corresponding isomers of Ura<>Ura and Me^1Ura<>Me^1Ura. Except for Cyt, which forms (t,a) Cyt<>Cyt in addition to the (t,s) isomer, the others yield only the (t,s) isomer. In F_3CCOOH, (t,a) Cyt<>Cyt is decomposed to Cyt, while syn dimers are stable. These Cyt<>Cyt derivatives display the AB or AA'BB' patterns in the NMR spectra, determined in F_3CCOOD at −2 °C. The mass spectra of these dimers resemble those of the corresponding monomer. N^4-unsubstituted dimers (U), Cyt<>Cyt and Me^1Cyt<>Me^1Cyt, have λ_{max} ~245 nm and ϵ_{max} ~10 000; N^4-monosubstituted dimers (M), Me^4Cyt<>Me^4Cyt and $Me_2{}^{1,4}$Cyt<>$Me_2{}^{1,4}$Cyt, have λ_{max} ~250 nm and ϵ_{max} ~15 000, and N^4-disubstituted dimers (D), $Me_2{}^{4,4}$Cyt<>$Me_2{}^{4,4}$Cyt and $Me_3{}^{1,4,4}$Cyt<>$Me_3{}^{1,4,4}$Cyt, have λ_{max} ~260 nm and ϵ_{max} ~20 000. These batho- and hyperchromic shifts indicate that the amino form is predominant in D and the imino form in U. In M both forms may be more evenly distributed. This assumption is further verified by the spectral characteristics of $Me_2{}^{1,3}$Cyt<>$Me_2{}^{1,3}$Cyt, which was synthesized because it could exist only in the imino form. IR and deuterated IR spectra were also studied (ν_{NH}/ν_{ND} = 1.33) in order to gather additional evidence for a possible amino–imino tautomerization for these Cyt<>Cyt derivatives in polar and nonpolar solvents. This information should be of importance to the photochemistry and photobiology of nucleic acids.

There is evidence to show that cyclobutane dipyrimidines containing cytosine [such as cytosine dimer (Cyt<>Cyt) or cytosine–thymine dimer (Cyt<>Thy)] are produced as photoproducts in DNA or polynucleotides by 280-nm irradiation[1] or possibly by photosensitized dimerization.[2] These Cyt-containing hetero- and homodimers were found[1] to be monomerized by shorter wavelength irradiation more easily than their corresponding Ura and Thy dimers and DNA

Table I. Preparation and Properties of N-Methylated Cyt<>Cyt

Cyt derivative	Registry no.	Acetone–water, %	Temp, °C	Irrad period, h	Derivative of Cyt<>Cyt Yield, %	mp, °C	R_f a	R_f b	R_f c
Cyt	71-30-7	67–33	3	50	18	>280	0.00	0.02	0.07
1-Me	1122-47-0	85–15	3	168	20	>280	0.02	0.06	0.21
N^4-Me	6220-47-9	85–15	3	96	42	>280	0.02	0.03	0.23
1,N^4-Me_2	6220-49-1	100–0	20	65	36	>280	0.03	0.15	0.23
$N^{4,4}$-Me_2	6220-48-0	95–5	3	168	86	275–278	0.07	0.44	0.50
1,$N^{4,4}$-Me_3	2228-27-5	100–0	20	72	14	260–268	0.13	0.55	0.46

[a] Silica gel with eluent B. [b] Cellulose with eluent B. [c] Cellulose with eluent A.

photolyase in the presence of visible light (photoreactivation), to inhibit in vitro nuclease activity and affect DNA synthesis like Thy<>Thy, and to be excised from the DNA of radiation-resistant bacteria at the same rate as Thy<>Thy. Despite the biological implications of these Cyt<>Cyt derivatives, their nature has not been fully characterized due to the fact that these compounds are exceedingly labile under general experimental conditions.[3-5] In order to clarify the detailed nature of various Cyt<>Cyt derivatives and this dimerization process, studies have been carried out with *N*-methylcytosine derivatives[6] and the cytosine nucleosides.[7] Due to the apparent stability of these *N*-methyl Cyt<>Cyt, it is possible to gain insight into the chemical characteristics of these dimers, and such knowledge can serve as a basis for a better understanding of Cyt dimers of nucleic acid components (in preparation).

Experimental Section

Syntheses of *N*-Methylcytosine Derivatives. Preparation of 4-Thiouracil (Sra). The compound was prepared according to the procedure of Ueda and Fox.[8]

***S*-Methyl-4-Thiouracil (Me^4Sra) and N^1,*S*-Dimethyl-4-Thiouracil ($Me_2^{1,4}$Sra).** These compounds were prepared according to the methods of Wheeler and Johnson.[9]

Preparations of Various N^4-Methylcytosine Derivatives. Me^4Cyt, $Me_2^{1,4}$Cyt, $Me_2^{4,4}$Cyt, and $Me_3^{1,4,4}$Cyt were prepared according to the methods reported in references 10–13, respectively.

Preparation of 1-Methylcytosine. Me^1Cyt was prepared according to the method of Fox and Shugar.[14]

Preparations of N^3-Methylcytosine Derivatives. Me^3Cyt was prepared according to the method of Brooks and Lawley.[15]

Irradiation of *N*-Methyl Derivatives of Cytosine. Irradiation Apparatus. These irradiators have been described previously[16] and are equipped with a bank of seven Sylvania fluorescent lamps F15T8/BL.

Irradiation Experiments. In Table I, the specific conditions are presented. The following is the general procedure. The compound was dissolved in acetone or acetone–water to give a 20 mM solution. This solution was transferred to quartz tubes and was flushed with argon for 30 min before irradiation. The tubes were sealed with paraffin films, and the irradiation was carried out either at ambient or cold room temperature. The dimer formed was deposited during the irradiation. It was collected by filtration and washed with acetone. The filtrate and acetone washes were combined. After concentration at reduced pressure, the residue was applied on preparative TLC plates (silica gel, 60F-254, Merck or 13254 cellulose, 6065, Eastman) and the eluents were (A) *n*-PrOH–water (10:3) and (B) chloroform–methanol–water (4:2:1) + 5% of methanol to the organic phase. The R_f values are listed in Table I.

Determination of Stereochemistry of Dimers. Deamination of *N*-Methylated Cytosine Dimers. Acid-catalyzed deamination of dimers was carried out with 5 mg of the dimers dissolved in 1 mL of 0.1 N HCl. The resulting solution was allowed to stand at room temperature for 48 h. The deposited crystals were collected. Its identification was established by spectral comparison with known stereoisomers of derivatives of Ura<>Ura.

C and N Methylation of Me^1Ura<>Me^1Ura to Form $Me_2^{1,3}$Thy<>$Me_2^{1,3}$Thy. This synthesis was accomplished with a novel procedure reported by Taguchi and Wang.[17]

Spectral Determinations. Ultraviolet and infrared (KBr pellets) absorption spectra were recorded on a Beckman Model DK-1 and a Perkin-Elmer Model 21 recording spectrophotometer, respectively. Nuclear magnetic resonance spectra were obtained on a Varian 220-MHz spectrometer. $(CD_3)_2SO$ was used as solvent at 22 °C; however, at −2 °C, CF_3COOD was used instead. $(CH_3)_4Si$ was the internal standard. Mass spectra were obtained on a CEC-21-110 mass spectrometer at 70 eV ionizing voltage and a source temperature of 250 °C.

Results and Discussion

It is well known that facile deamination occurs with dihydrocytosine (hCyt) derivatives.[18] Because of the instability, studies involving hCyt compounds are, in general, perplexing. In photochemical studies, photohydration of Cyt derivatives has proved to be problematic in the isolation of the product, a ho^{6}hCyt derivative.[19] This predicament again has impeded the progress in the studies of photodimerization of Cyt derivatives. In order to gain a satisfactory understanding of the nature of Cyt dimers (Cyt<>Cyt), acetone-sensitized photodimerization studies of *N*-methyl-substituted Cyt derivatives have been carried out. The advantage of selecting these derivatives is twofold. First, N^1-methyl derivatives are analogues of biologically active compounds, Cyd, dCyd, or CMP; and, second, N^4-methyl derivatives may afford information concerning an important issue, i.e., the nature of amino–imino tautomerism of the C^4–NH_2 moiety in the Cyt<>Cyt and possibly hCyt derivatives in general.

Photosensitized dimerization of the Cyt derivatives in the presence of acetone with mainly 313-nm light gave cyclobutyl dicytosines (cytosine dimers, Cyt<>Cyt) as expected. Unexpectedly, we often found that crystals of a pure stereoisomer deposited directly from reaction solutions. This is indeed an added advantage in using these MeCyt derivatives as model compounds and has facilitated our study. The product yields of these various dimers and their respective R_f values are given in Table I.

Determinations of the stereoconfigurations of these Cyt dimers required an approach that is outlined below. This

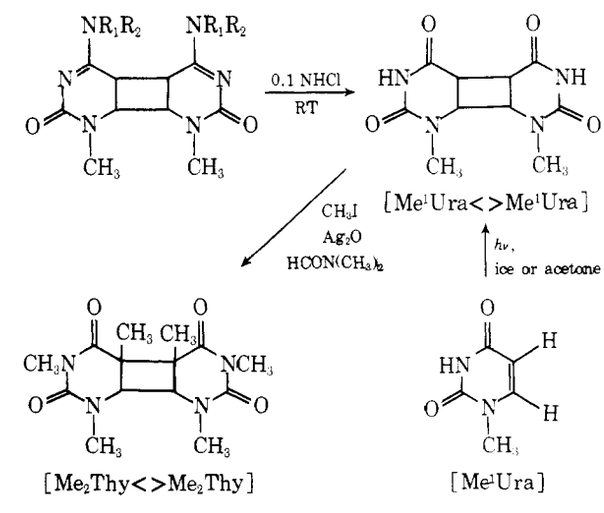


Table II. Acid-Catalyzed Deamination and Splitting of Various Cyt<>Cyt and Related Dimers

Dimer	Product	Stereoconfiguration	Yield, % In 0.1 N HCl	Yield, % In F_3CCOOH
Cyt<>Cyt	Ura<>Ura	(t,s),(t,a)	33, 53[a]	31 (45% Cyt)[b]
Me^1Cyt<>Me^1Cyt	Me^1Ura<>Me^1Ura	(t,s)	57	
Me^4Cyt<>Me^4Cyt	Ura<>Ura	(t,s)	70	70
$Me_2^{1,4}$Cyt<>$Me_2^{1,4}$Cyt	Me^1Ura<>Me^1Ura	(t,s)	75	60
$Me_2^{4,4}$Cyt<>$Me_2^{4,4}$Cyt	Ura<>Ura	(t,s)	62	
$Me_3^{1,4,4}$Cyt<>$Me_3^{1,4,4}$Cyt	Me^1Ura<>Me^1Ura	(t,s)	72	82
Me^1Ura<>Me^1Ura	No change	All four		
Ura<>Ura	No change	All four		

[a] Estimated from IR spectral data. [b] Anti dimers decompose in strong acid media to the monomer.

Table III. Chemical Shifts of N-Methylated Cyt<>Cyt

Dimer	Chemical shifts (δ, ppm from Me_4Si) N^1CH_3 (s)	N^4CH_3 (s)	C^5H (d) [J][b]	C^6H (d) [J]
Cyt<>Cyt			4.57 (dd)[c] 4.76 [7]	5.12 (dd)[c] 4.85 [7]
Me^1Cyt<>Me^1Cyt				
Me^4Cyt<>Me^4Cyt		3.44	4.73 [7]	4.88 [7]
$Me_2^{1,4}$Cyt<>$Me_2^{1,4}$Cyt	3.30	3.42	4.64 [7]	4.86 [7]
$Me_2^{4,4}$Cyt<>$Me_2^{4,4}$Cyt		3.65, 3.69	4.50 [6]	5.32 [6]
$Me_3^{1,4,4}$Cyt<>$Me_3^{1,4,4}$Cyt	3.29	3.60, 3.64	4.50 [6]	5.36 [6]
	3.00[a]	2.83[a]	3.74 [6][a]	4.03 [6][a]

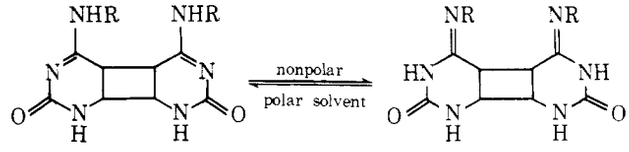
[a] These values were estimated at 22 °C in $(CD_3)_2SO$ and the other values were determined at −2 °C in F_3CCOOH. [b] Coupling constants are given in brackets and in Hz. [c] These chemical shifts are for the (t,a) isomer, but all the others are for the (t,s) isomer.

approach necessitated the study of Me^1Ura photodimerization (Taguchi and Wang, in preparation) and the development of a new method of C-alkylation of Pyr<>Pyr.[17] Alternatively, structural elucidation by means of x-ray diffraction analysis of a single crystal can be used.[20] In pursuing this chemical approach, several interesting findings were also noted and are being reported elsewhere. Apparently, under the mild conditions for deamination (Table II), Cyt<>Cyt were converted to the corresponding Ura<>Ura in fair yields and, at the same time, we found that all four isomers of Ura<>Ura and of Me^1Ura<>Me^1Ura were not affected. On the other hand, with trifluoroacetic acid similar results were obtained for the syn isomers of Cyt<>Cyt, but anti isomers were split quantitatively to the corresponding monomers. Except Cyt<>Cyt, only the (t,s) isomer was obtained for all five N-methylated Cyt<>Cyt. This finding agrees with that observed in photosensitized dimerization of Me^6Ura.[21] Such (t,s) isomer formation was shown not to be influenced by the solvent dipole moments. Therefore, the possibility that a $^3\pi^*,\pi$ complex or a collision complex having a head to head or syn arrangement precedes the formation of the dimers and determines their configurations should be considered. This suggestion was made[22] for cyclic enones; however, it seems not only applicable to Me^6Ura but also for Cyt derivatives having a somewhat different ground-state electronic configuration.

The NMR spectra of these dimers are given in Table III. These dimeric molecules have at least one symmetry axis; therefore, the AB or AA′BB′ patterns displayed are those expected. Because of the low solubility of the dimers in $(CH_3)_2SO$, F_3CCOOD had to be used for NMR determinations. In order to avoid acid-catalyzed splitting of these dimers at room temperature, −2 °C was maintained during the study. However, (t,s) isomers were proved to be the only photoproduct in these reactions and this precaution was, in effect, not imperative. As expected, there was considerable upfield shift for these signals in neutral solvent as seen in $Me_3^{1,4,4}$Cyt<>$Me_3^{1,4,4}$Cyt which has sufficient solubility in $(CH_3)_2SO$.

The mass spectra of these dimers resembled those of the corresponding monomers. Apparently, cleavage across the cyclobutane ring of the dimers generates abundant ions, and subsequent fragmentation of which are equivalent to the respective ionized monomers.[23]

The UV spectral data of these dimers are listed in Table IV. Both the solvent and pH effects have been studied. Two features are apparent: one is the ~5-nm bathochromic or red shift of λ_{max} for each N^4CH_3 group and the other is the ~5000 hyperchromic effect of ϵ_{max} also for each N^4CH_3 substituent. Therefore, these dimers were divided into three categories: N^4 unsubstituted (U), N^4 monosubstituted (M), and N^4 disubstituted (D) for our consideration. The reported values of λ_{max} and ϵ_{max} of hCyt (239 nm, 11.3×10^3) and Me^1hCyt (243 nm, 10.5×10^3)[24] may serve as the basis. Because U can be considered as derivatives of hCyt with substituents on C^5 and C^6, one would expect slight bathochromic shifts as have been observed. However, the *molar* extinction coefficient (ϵ_{max}) for U should double that of the monomeric hCyt because each dimeric molecule contains two identical chromophores. Yet, the ϵ_{max} values estimated were only ~10 000 for U rather than ~20 000 as expected. For M, λ_{max} are shifted as anticipated and ϵ_{max} at ~15 000 are again lower than those expected. Distinctively, in the cases of D, both ϵ_{max} and λ_{max} observed are as anticipated. This suggests that only D may possess the same chromophore as the monomeric hCyt and Me^1hCyt. One obvious possibility is the amino–imino tautomeric equilibrium, as shown, which could occur with U and M but not with



amino form imino form

D. This possibility was considered in the cases of hCyt and Me^1hCyt monomers.[24] From the pK_a value of Me^1hCyt in aqueous solution, these authors estimated the amino–imino

Table IV. UV Spectra of N-Methylated Cyt<>Cyt

Dimer	Registry no.	Concn (mM)	λ_{max} (nm)	$\epsilon_{max} \times 10^{-3}$	Solvent [pH]
		N^4 unsubstituted (U)			
Cyt<>Cyt	64161-45-1	0.073	*243*[a]	10.4	H_2O [9.01]
			243	10.3	H_2O [7.02]
			(219)[b]	(8.65)	H_2O [2.03]
					CH_3OH
Me^1Cyt<>Me^1Cyt	64103-42-0	0.064	*246*	9.56	H_2O [9.03]
			246	8.85	H_2O [7.05]
			(219)	(8.42)	H_2O [2.02]
			end absorption		CH_3OH
		N^4 monosubstituted (M)			
Me^4Cyt<>Me^4Cyt	64082-05-9	0.069	248	15.1	H_2O [9.04]
			235	13.4	
		0.033	*248*	14.1	CH_3OH
			234	15.0	
$Me_2^{1,4}$Cyt<>$Me_2^{1,4}$Cyt	64082-06-0	0.088	253	14.8	H_2O [9.01]
			236	12.5	
		0.076	*252*	14.4	CH_3OH
			234	14.6	
		0.038	*249*	9.67	CH_3CN
			233	14.1	
		N^4 disubstituted (D)			
$Me_2^{4,4}$Cyt<>$Me_2^{4,4}$Cyt	64082-08-2	0.052	258	19.1	H_2O [9.00]
		0.039	257	20.0	CH_3OH
		0.054	253	19.5	CH_3CN
$Me_3^{1,4,4}$Cyt<>$Me_3^{1,4,4}$Cyt	64082-07-1	0.031	263	18.8	H_2O [9.01]
		0.045	261	19.8	CH_3OH
		0.030	255	19.8	CH_3CN

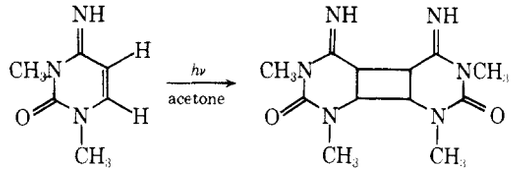
[a] λ_{max} in italics indicates a shoulder in the spectra. [b] The values given in parentheses are approximate because acid-catalyzed deamination is likely to occur.

tautomeric constants to be approximately 25, greatly in favor of the amino form.

Consequently, one may conclude that hCyt moieties in dimers are likely to have λ_{max} >240 nm with ϵ_{max} ~20 000, if they should exist in the amino form. On the other hand, if both are present in the imino form these dimers should have λ_{max} <230 nm with ϵ_{max} ~10 000. Thus, in aqueous media, it is probable that the amino form is predominant in D and the imino form exists largely in U. In M, both forms may be more evenly distributed.

In less polar solvents, CH_3OH and CH_3CN, an hypochromic effect in the 250-nm region for U and M is apparent. The effect results in the appearance of only end absorption or a decrease in ϵ_{max}. On the contrary, little change in ϵ_{max}'s was observed for D, although there is certain blue or hypsochromic shift. This shift is a trend expected for a $\pi\pi^*$ band in less polar solvents.[25] Any decrease in ϵ in the 250-nm region with a concomitant increase in the <230-nm region may be interpreted as evidence of a shift of equilibrium from an amino to an imino form. Thus, we may assume that the contribution of the imino form in the dimers would increase with decreasing polarity of the media.

For verification of this assumption, photosensitized dimerization of $Me_2^{1,3}$Cyt was carried out. With the N^3–CH_3 group, this monomeric compound could exist only in the imino form, as shown. Although $Me_2^{1,3}$Cyt in an ethanolic solution



gives rise to a UV spectrum with λ_{max} at 223 and 273 nm and ϵ_{max} of 10 000 and 8500, respectively, its reduced product $Me_2^{1,3}$hCyt in an aqueous solution has λ_{max} 227 nm with ϵ_{max} 12 000. As expected, $Me_2^{1,3}$Cyt<>$Me_2^{1,3}$Cyt, which could exist only in the imino form, has an ϵ_{max} of 9000 at 228 nm in water. In both CH_3OH and CH_3CN, this dimer shows only end absorption. This observation corroborates our interpretation of UV spectra of these dimers.

A study of the infrared spectra of these dimers was also undertaken to gather additional evidence for this amino–imino tautomerization. In principle, on deuteration of an imino–NH band, it would shift to a lower frequency with an isotopic ratio, ν_{NH}/ν_{ND}, of 1.375.[26] This method has been used for the study of such a tautomerization in heterocyclic systems.[27] For Cyt derivatives, the isotopic ratios of this shift were found to be in the range of 1.30–1.36.[26] For Me^3Cyt<>Me^3Cyt, a shift with a ratio of 1.33 was observed for the $=N^4H$ stretching band (2976 cm^{-1} in $CDCl_3$; 2960 cm^{-1} in a KBr pellet) and the corresponding $=N^4D$ band (2242; 2222 cm^{-1}). Similar shifts are evident in the spectra of Cyt<>Cyt (3021 to 2255 cm^{-1}) and of Me^1Cyt<>Me^1Cyt (2976 to 2252 cm^{-1} in Nujol).

In summary, a number of rather "stable" Cyt<>Cyt derivatives have been prepared, thus permitting the study of their UV absorption spectra. Interestingly, the observation that solvent polarity changes cause a change in the tautomeric equilibrium is unusual, as is the finding that an imino form in heterocyclic compounds is capable of a tautomeric shift to an amino form.[28] However, since the tautomeric constant for 5,6-saturated Cyt derivatives is relatively small,[28] the observed shift can be appreciated. In addition, IR, mass, and NMR spectra have also been examined. Such knowledge was not available previously with Cyt<>Cyt derivatives and affords further information concerning the characteristics of these compounds. Specifically, the possible amino–imino tautomerization of these dimers is of interest not only to chemical studies but also to biological considerations. If such a tautomerization should take place in the biological microenvironment, it could result in miscoding or in facile deamination

causing the conversion of Cyt to Ura even after enzymatic repair. Furthermore, the configuration of these dimers was determined to be trans with the trans–syn isomer as the only or the predominant product. If a cis–syn isomer should form as reported,[4,5] in the study of Cyd and dCyd, its acid-catalyzed deamination product, cis–syn Ura<>Ura, should be extremely stable and easily identifiable. The information concerning the stereoconfiguration of these dimers is of particular importance when related to the photochemistry of nucleic acids.[29–33]

References and Notes

(1) R. B. Setlow and W. L. Carrier, *J. Mol. Biol.*, **17**, 237 (1966).
(2) R. Ben-Ishi, E. Ben-Hur, and Y. Hornfeld, *Isr. J. Chem.*, **6**, 769 (1968).
(3) A. J. Varghese and C. S. Rupert, *Photochem. Photobiol.*, **13**, 365 (1971).
(4) A. J. Varghese, *Biochemistry*, **10**, 2194 (1971).
(5) A. J. Varghese, *Photochem. Photobiol.*, **15**, 113 (1972).
(6) H. Taguchi, B. S. Hahn, and S. Y. Wang, 2nd Annual Meeting American Society of Photobiology, Vancouver, B.C., July 1974, p 21.
(7) B. S. Hahn, H. Taguchi, and S. Y. Wang, *Radiat. Res.*, **59**, 105 (1974).
(8) T. Ueda and J. J. Fox, *J. Med. Chem.*, **6**, 697 (1963).
(9) H. L. Wheeler and T. B. Johnson, *Am. Chem. J.*, **42**, 30 (1909).
(10) T. Ueda and J. J. Fox, *J. Org. Chem.*, **29**, 1770 (1964).
(11) G. W. Kenner, C. B. Reese, and A. R. Todd, *J. Chem. Soc.*, 855 (1955).
(12) I. Wempen, R. Dushinsky, L. Kaplan, and J. J. Fox, *J. Am. Chem. Soc.*, **83**, 4755 (1961).
(13) A. R. Katritzky and A. J. Waring, *J. Chem. Soc.*, 3046 (1963).
(14) J. J. Fox and D. Shugar, *Biochim. Biophys. Acta*, **9**, 369 (1952).
(15) P. Brooks and P. D. Lawley, *J. Chem. Soc.*, 1348 (1962).
(16) S. Y. Wang, *J. Am. Chem. Soc.*, **80**, 6196 (1958).
(17) H. Taguchi and S. Y. Wang, *J. Org. Chem.*, **42**, 3321 (1977); cf. ref 31.
(18) M. Green and S. S. Cohen, *J. Biol. Chem.*, **228**, 601 (1957).
(19) G. DeBoer and H. E. Johns, *Biochim. Biophys. Acta*, **204**, 18 (1970).
(20) I. L. Karle, in "Photochemistry and Photobiology of Nucleic Acids, Chemistry", Vol. 1, S. Y. Wang, Ed., Academic Press, New York, N.Y., 1976, Chapter 11, p 483.
(21) M. N. Khattak and S. Y. Wang, *Tetrahedron*, **28**, 945 (1972).
(22) E. J. Corey, J. D. Bass, R. LeMahieu, and R. B. Mitra, *J. Am. Chem. Soc.*, **86**, 5570 (1964).
(23) C. Fenselau, in "Photochemistry and Photobiology of Nucleic Acids, Chemistry", Vol. 1, S. Y. Wang, Ed., Academic Press, New York, N.Y., 1976, Chapter 9, p 420.
(24) D. M. Brown and M. J. E. Hewlins, *J. Chem. Soc. C*, 2050 (1968).
(25) M. Kasha, in "Light and Life", W. D. McElroy and B. Glass, Ed., Johns Hopkins University Press, Baltimore, Md., 1961, p 31.
(26) C. L. Angell, *J. Chem. Soc.*, 504 (1961).
(27) R. T. C. Brownlee, A. R. Katritzky, and R. D. Topom, *J. Chem. Soc.*, 726 (1966).
(28) A. R. Katritzky and J. M. Lagowski, *Adv. Heterocycl. Chem.*, **1**, 339 (1963).
(29) A. J. Varghese and S. Y. Wang, *Nature (London)*, **213**, 909 (1967).
(30) D. Weinblum, *Biochem. Biophys. Res. Commun.*, **27**, 387 (1967).
(31) H. Taguchi and S. Y. Wang, *Biochem. Biophys. Res. Commun.*, **73**, 356 (1976).
(32) M. H. Patrick and R. O. Rahn, in "Photochemistry and Photobiology of Nucleic Acids, Biology", Vol. 2, S. Y. Wang, Ed., Academic Press, New York, N.Y., 1976, Chapter 2, p 35.
(33) G. Fisher and H. E. Johns, in "Photochemistry and Photobiology of Nucleic Acids, Chemistry", Vol. 1, S. Y. Wang, Ed., Academic Press, New York, N.Y., 1976, Chapter 4, p 169.

Diterpenoid Total Synthesis, an A → B → C Approach. 12. Aromatic C Rings without Alkyl Substituents. Model Systems for Podocarpic Acid and Diterpenoid Alkaloids[1]

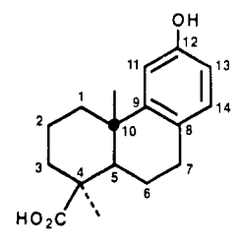
Walter L. Meyer,* Carl W. Sigel,[1d] R. John Hoff,[1e] Thomas E. Goodwin,[1f] Richard A. Manning, and Patricia G. Schroeder

Department of Chemistry, University of Arkansas, Fayetteville, Arkansas 72701

Received May 17, 1977

Examination of the general sequence **2** → **7** for addition of a 13-unsubstituted phenolic C ring[2] to decalones **2a–e** is described. Condensation of the decalones with HCO_2Et is uniformly efficient, but the rates and yields for conversion of the 8-hydroxymethylene derivatives to 8-formyl-Δ^8-7-octalones by reaction with DDQ vary remarkably. Addition of the sodium enolate of $MeCOCH_2CO_2$-*t*-Bu to α-formyl enones **4a–d** and acid-catalyzed cyclization of the adducts **5a–c** to tricyclic enediones **6a–c** proceed normally and in high yield. Aromatization of **6a–c** by $pyHBr_3$ affords not only 7-keto-12-phenols (**7**), the sole products from their 13-alkyl analogues, but also 13-bromo-7-keto-12-phenols and, at least in the case of **6a**, 13-bromo-Δ^{13}-7,12-enediones (**9**). Dehydrohalogenation of **9a** by collidine produces **7a**, a podocarpic acid model. Hydrogenolysis of the 12-(2′-benzoxazolyloxy) derivative of **7b** provides tetracyclic amide **19**, which has been formally converted to several diterpenoid alkaloids.[15]

Total syntheses of several C-aromatic perhydrophenanthrene diterpenoids have demonstrated the efficiency of the general sequence **2** → **7** (Scheme I) for constructing a substituted aromatic ring at carbons 8 and 9 of a *trans*-7-decalone.[1a,2–4] A C-13 alkyl substituent (R^4) has been an important component of all the natural products we have previously prepared by this route, and we consider that one of the significant advantages of this synthetic procedure is its ability to include introduction of that group as an integral part of the annulation process. However, certain diterpenoids such as podocarpic acid (**1**) are devoid of such C-ring substitution, and this might also be true of other structures for which use of this ring elaboration plan would be desirable. Investigations reported here show that the synthesis is equally applicable to structures in which R^4 = H, but that modifications of the sequence may be necessary. They also reveal some unexpected effects of structure on the reaction of an α-hydroxymethylene ketone with DDQ (**3** → **4**). These conclusions result primarily from research into the synthesis of model compounds in the podocarpic acid and diterpenoid alkaloid series.



1

The decalones which were used in this work, **2a–e**, have been reported earlier,[5,6] and their condensation with ethyl formate is unexceptional. However, dehydrogenation of these hydroxymethylene ketones by DDQ under conditions which have given 75–95% yields of α-formyl enones **4** in other