potential of such quinones would be lowered and electron transfer reduced.[9]

The synthetic methodology outlined in this manuscript provides potentially the simplest route to 2,5-disubstituted 1,4-benzoquinones and complements recent advances directed toward the monoalkylation or arylation of the quinone nucleus. Particularly noteworthy in this regard are the utilization of trimethylsilyl cyanide (TMSCN) protected quinones,[10] the use of lithium salts of 1-bromo-3,3,6,6-tetramethoxy-1,4-cyclohexadiene (a latent quinone carbanion),[11] the reactions of quinones or protected bromoquinols with π-allyl–nickel complexes,[12] the utilization of monoketals of quinones,[13] and the use of 1,4-dimethoxynaphthyllithium.[14]

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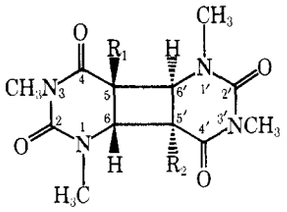
C-Alkylation and Deuterium Exchange of Cyclobutane–Dipyrimidines

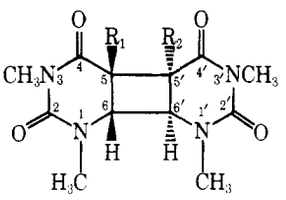
Summary: A novel method for C-alkylation and deuteration of pyrimidine dimers with retention of configuration is described.

Sir: Generally, it is agreed[1-5] that the most significant breakthrough in nucleic acid photochemistry was the isolation and identification of the thymine dimer (Thy<>Thy)[6] by Beukers and Berends[7] and by Wang.[8] As pyrimidine (Pyr) photodimerization has gained significance in biological systems,[9,10] it has become one of the most intensively studied topics.[11] However, reports concerning studies of the chemistry of Pyr dimers are infrequent.[2,12]

N-Methylation of uracil dimer (Ura<>Ura) was first found[13] to give primarily Me^3Ura<>Me^3Ura. With dimethyl sulfate and diazomethane, Ura<>Ura yielded a mixture of di- and trimethyl derivatives.[2] However, complete methylation was obtained when *cis,syn-* and *cis,anti-*Ura<>Ura were treated with methyl iodide and silver oxide in dimethylformamide.[14] Finally, the complete methylation of



I(trans,anti)



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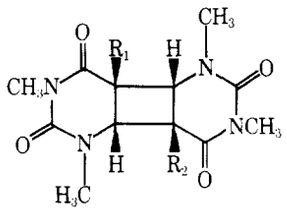
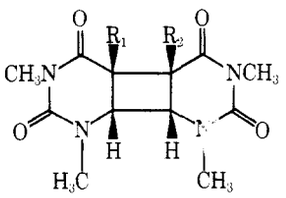


III(cis,anti)



IV(cis,syn)

a, $R_1 = R_2 = H$	Me_2Ura<>Me_2Ura
b, $R_1 = CH_3$; $R_2 = H$	Me_2Thy<>Me_2Ura
c, $R_1 = CH_3$; $R_2 = CH_3$	Me_2Thy<>Me_2Thy
d, $R_1 = CH_2CH_3$; $R_2 = H$	Me_2EtUra<>Me_2Ura
e, $R_1 = R_2 = CH_2CH_3$	Me_2EtUra<>Me_2EtUra
f, $R_1 = R_2 = C_6H_5CH_2$	Me_2BzUra<>Me_2BzUra
g, $R_1 = R_2 = D$	Me_2d_1Ura<>Me_2d_1Ura

the four isomeric Ura<>Ura to their corresponding Me_2Ura<>Me_2Ura was found to be feasible in dimethyl sulfoxide.[15]

Unexpectedly, we discovered that subsequent to complete N-methylation, C-methylation occurred when *trans,syn-* and *trans,anti-*Ura<>Ura were treated under similar conditions. This finding prompted us to investigate further the C-alkylation of cyclobutane derivatives.

The general procedure for C-alkylation was as follows. First, silver oxide (2 mmol, 460 mg) was added to a solution of Me_2Ura<>Me_2Ura (0.2 mmol, 56 mg) in $HCON(CH_3)_2$ (2 mL). To this mixture, 12 mmol of an alkyl halide was added; this was stirred for an appropriate period at ambient temperature. This reaction mixture was then poured into 200 mL of 5% NaCN solution to decompose the "silver complex".[16] The product was extracted three times with 200 mL of chloroform. Chloroform was evaporated from the combined extracts, and the residue was applied on silica gel thin-layer plates for chromatography with an eluent of chloroform/acetone (2:1). We found that the R_f values for dialkylated compounds are greater than the value of the monoalkylated products which, in turn, are greater than those of the starting materials. For this reason, these product mixtures were easily separated. The product was then eluted with methanol and recrystallized. The reaction conditions and the properties of the alkylation products are summarized in Table I.

We found that C-methylation of cis isomers is slower than for trans isomers (see Table I). This appears to correlate with our observation in deuterium exchange of the dimers. In this process, a solution of a dimer in D_2O was treated with 2 molar equiv. of silver oxide at ambient temperature with stirring for 24 h, and the insoluble material was removed by filtration. The deuterated product was then extracted from the filtrate with chloroform. After being dried over anhydrous Na_2SO_4, chloroform was evaporated. The residue was dissolved in $CDCl_3$ for the NMR analysis of the extents of deuteration. As can be seen from Table II, deuterated Ia and IIa both showed only three singlets, with the disappearance of the signal corresponding to C(5)H. This clearly indicates that "complete"deuteration at C(5) to C(5)D occurred. However, after similar deuterium exchange, IIIa and IVa gave quite complex spectra showing a pair of "pseudo" triplets for C(5)H and C(6)H. This evidence suggests that cis dimers were only par-

Table I. Alkylation of $Me_2Ura<>Me_2Ura$ at Room Temperature in Dimethylformamide

$Me_2Ura<>Me_2Ura$	RI	Reaction time, h	Product	Yield, %	Solvent for crystallization	Mp, °C
trans,anti (Ia)	CH_3	24	Ic	92	CH_3OH	259–260[e]
	C_2H_5	96	Id	24	AcOEt[d]	180
			Ie	31	CH_3OH	sublime
	$C_6H_5CH_2$[a]	24	If[c]	34	CH_3OH	>270
trans,syn (IIa)	CH_3	24	IIc	86	CH_3OH	253–254[e]
	C_2H_5	96	IId	42	AcOEt	182–183
			IIe	13	C_2H_5OH	sublime
	$C_6H_5CH_2$[a]	24	IIf[c]	39	CH_3OH	273
cis,anti (IIIa)	CH_3	48[b]	IIIb	27	AcOEt	208–209
			IIIc	4	CH_3OH	226–227[e]
cis,syn (IVa)	CH_3	48[b]	IVb	32	AcOEt	206–207
			IVc	<2	CH_3OH	252–253[e]

[a] Benzyl bromide was used instead of iodide. [b] Equal portions of the reagents were added at 6-, 18-, and 24-h intervals. [c] Mother liquors after recrystallization were not studied. [d] Petroleum ether was added for recrystallization. [e] These melting points are comparable to those reported by Kleopfer and Morrison.[19]

Table II. NMR Spectra of $Me_2Ura<>Me_2Ura$ [220 MHz, 25 °C, $CDCl_3$ solvent, $Si(CH_3)_4$ internal standard]

	Chemical shift, δ, ppm					
	Nondeuterated			Deuterated		
$Me_2Ura<>Me_2Ura$	$N(CH_3)$[6 H, s]	C(5)H[2 H, s]	C(6)H[2 H, s]	$N(CH_3)$	C(5)H	C(6)H
trans,anti	3.16	3.56	4.14	3.11 (6 H, s)	No	4.11 (2 H, s)
Ia → Ig	3.31	(3.43)[a]	(4.18)[a]	3.27 (6 H, s)		
	(3.13)[a]	(3.52)[b]	(4.10)[b]			
	(3.3)[a]					
trans,syn	3.09	3.73	3.88	3.09 (6 H, s)	No	3.89 (2 H, s)
IIa → IIg	3.27	(3.72)[a]	(3.92)[a]	3.27 (6 H, s)		
	(3.12)[a]	(3.63)[b]	(3.90)[b]			
	(3.3)[a]					
cis,anti	3.14	3.77	4.11	3.14 (s)	3.79 (t)[d]	4.12 (t)[d]
IIa → IIIg	3.16	(3.79)[b]	(4.12)[b]	3.16 (s)		
	(3.17)[a]	(3.98)[a,c]	(3.98)[a,c]			
cis,syn	3.02	3.78	4.08	3.02 (s)	3.79 (t)[d]	4.08(t)[d]
IVa → IVg, IVa	3.19	(3.80)[b]	(4.08)[b]	3.18		
	(3.1)[a]	(3.72,	(4.06,			
	(3.22)[a]	3.80,	4.14,			
		3.88)[a]	(4.22)[a]			

[a] Values reported by Elad et al.[14] [b] Values given were calculated from those reported by Fahr et al.,[20] and the NMR spectra were measured with a 90-MHz spectrometer. [c] These signals appeared as a multiple centered at δ 3.98. The correlation between the NMR patterns of C(5)H and C(6)H of $Me_2Ura<>Me_2Ura$, $Me_2Thy<>Me_2Ura$, and $Me_2Thy<>Me_2Thy$ are quite interesting. Their interpretations and possible importance in the assignments of various stereoisomers of homo and hetero dimers have been reported.[21] [d] These signals are due to a combination of doublet and singlet of un- and dideuterated species.

tially deuterated because these triplet signals can be assigned to both the deuterated and the nondeuterated starting materials (see Table II). This difference between cis and trans isomers can be attributed to the variance in anion formation at the exchange sites, i.e., the sites of alkylation. Thus, it is reasonable to suggest that the ease of anion formation at methylation sites is responsible for the difference in C-methylation of cis and trans dimers.

Under the condition of complete C-methylation of these dimers, only partial ethylation and benzylation were obtained, even for trans isomers. These results are also presented in Table I. However, attempts to introduce isopropyl or *tert*-butyl groups have been unsuccessful so far.

Although alkylation and deuteration have not been detected previously for Pyr dimers, our finding that these processes occur with ease was not entirely unexpected. An earlier study[17] of the effects of ring size on the rates of base-catalyzed enolization of cycloalkanones showed that the reactivity is 4 > 5 > 6 > 7 in $HCON(CH_3)_2$–D_2O. Indeed, we find that neither methylation nor deuteration takes place when 5,6-dihydro derivatives of the six-membered ring compounds Me_2Ura and Me_2Thy are subjected to the same conditions. However, the possibility that the *trans*-dihydropyrimidine ring, which is on the same side as the proton being removed, may help form a complex with the Ag_2O that may facilitate this reaction should also be considered.[18]

Since the stereochemistry of various isomers of $Me_2Ura<>Me_2Ura$ and $Me_2Thy<>Me_2Thy$ has been well established[19] and, as we have shown, C-methylation of $Me_2Ura<>Me_2Ura$ isomers resulted in the respective $Me_2Thy<>Me_2Thy$ isomer with the same configuration, this methylation process must take place with the retention of configurations.

The importance of the above findings may be indicated by several reasons. Obviously, they furnish information enabling a better understanding of the correlation of Pyr<>Pyr. This approach of C-alkylation provides a convenient method for the preparation of various isomers of Thy<>Ura derivatives,[21] one of which has been implicated as a product isolable from the acid hydrolysates of UV-irradiated DNA *in vivo* and *in vitro*.[22] In addition, the susceptibility of deuterium exchange is being developed as a sensitive method for assaying various uracil homo and hetero dimers in the presence of Thy<>Thy by tritium labeling of photoproducts of UV-irradiated DNA and RNA. Although all of the above specifies aspects that have direct relevance to the studies of photobiology of nucleic acids, this reaction may be pertinent with regard to alkylation of cyclobutane derivatives in general. The latter study has much current interest.[23]

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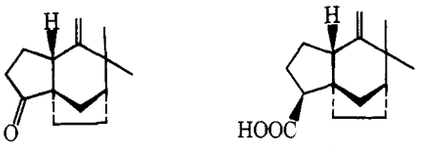
The Synthesis of Khusimone

Summary: A biogenetically patterned synthesis of khusimone (**1**), a norsesquiterpene with zizaene skeleton, proceeds through the two epimeric tricyclic ketones **14** and **15**, prepared by intramolecular Diels–Alder cyclization of the trienone ketal **13**. Acid-catalyzed isomerization of **15** gives exclusively isokhusimone (**17**), while isomerization of epimer **14** yields norcedrenone (**16**) and isokhusimone (**17**) in a ratio of 2:1. To convert isokhusimone (**17**) to the less stable racemic khusimone (**1**), the allylic alcohol **21** produced on photooxygenation of **17** is reduced with zinc and hydrogen chloride in ether.

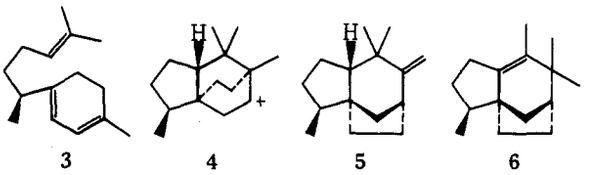
Sir: Vetiver oil [*Vetiveria zizanioides* (L.) Nash] is one of the important raw materials for the composition of refined fragrances. The characteristic scent of the essence is partly due to khusimone (**1**), a tricyclic norsesquiterpene ketone.[1] Oxidative decarboxylation of *natural* zizanoic acid (**2**) with lead tetraacetate, followed by oxidation of the resulting secondary alcohol, has been utilized[2] to produce quantities of khusimone (**1**), but the two published *total* syntheses[3] of zizanoic acid (**2**) are unfortunately not practicable.

We describe a total synthesis of khusimone (**1**), which in its critical stages mimics the most likely biogenetic pathway.



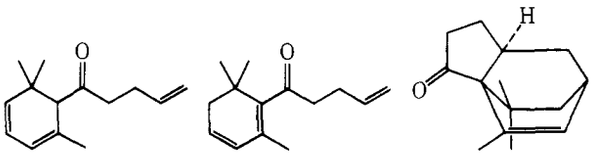
1 **2**

Yoshikoshi[4] was the first to suggest that zizaenes might biogenetically be derived from γ-curcumene (**3**) via the ion **4**, followed by two Wagner–Meerwein rearrangements. The subsequent discovery of prezizaene (**5**),[5] its acid-catalyzed isomerization to, among other products, isozizaene (**6**), and the very inefficient dehydration of allocedrol (secondary alcohol derived from **4**) to *enantio*-prezizaene[6] provided indirect evidence in support of this biogenetic scheme.



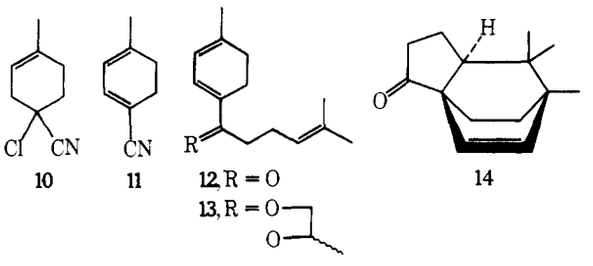
3 **4** **5** **6**

Our plan to construct the critical tricyclic olefin **14** or **15** by an intramolecular Diels–Alder reaction was based on the previously observed thermal cyclization of **7** to **9** (70% yield), which seems to proceed via the hypothetical intermediate **8**, the product resulting from a 1,5-hydride shift.[7]

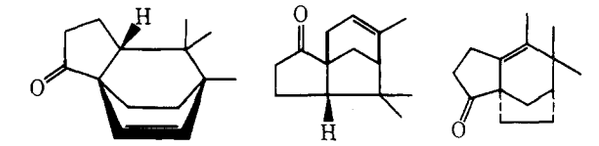


7 **8** **9**

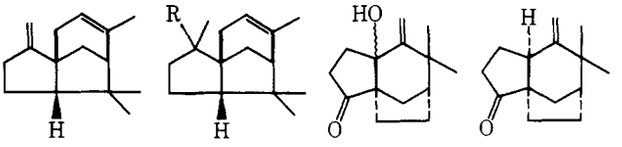
Addition of isoprene to α-chloroacrylonitrile[8] in the presence of some 2,5-di-*tert*-butylhydroquinone (15 h, 100 °C) gave the adduct **10** accompanied by 30% of its isomer. In preparative runs these were not separated, and the mixture was treated with 1,5-diazabicyclo[3.4.0]non-5-ene in tetrahydrofuran at 0–5 °C. Fractional distillation afforded the pure nitrile **11**, UV max (95% EtOH) 295 nm (ε 9950), in 55% overall yield. Condensation of **11** with 5-lithio-2-methylpent-2-ene, prepared from the corresponding bromide[9] and lithium con-



10 **11** **12**, R = O; **13**, R = O— **14**



15 **16** **17**



18 **19**, R = α-H; **20**, R = β-H **21** **22**