(8a)-C(4a)-C(4) 71.4(2)°. The atoms C(1), C(3), N(2), C(9), O(12), and O(10) lie in a plane with a maximum deviation of 0.022 (2) Å at N(2): C(11) deviates only by 0.063 (3) Å from the plane. The N(2)-C(9) length (1.343 (3) Å) is close to a typical C-N bond length found in peptides.

(1*S*,4*R*,8*R*)-*trans*- and (1*S*,4*S*,8*R*)-*cis*-1,3,4,4a,5,7,8,8a-Octahydro-1-isopropyl-2-(*p*-tolylsulfonyl)-6(2*H*)-isoquinolone (20a and 20b). The Diels-Alder reaction of **3b** was performed in the same way as that described for **3a** to give a mixture of **20a** and **20b** in 70% yield: IR ($CHCl_3$) 3005, 2960, 1710, 1325, 1145 cm^{-1}; exact mass calcd for $C_{19}H_{28}NO_3S$ 350.1790 (M^+ + H), found 350.1784. Separation of **20a** and **20b** was achieved by medium-pressure liquid chromatography (Develosil 60 prepacked column, hexane-AcOEt (3:1)).

20a: mp 121.1-127.0 °C; $[\alpha]^{24}_D$ +18.1° (*c* 0.93, $CHCl_3$); ^1H NMR (500 MHz) δ 0.88 (d, *J* = 6.7 Hz, 3 H, CH_3), 1.01 (d, *J* = 6.7 Hz, 3 H, CH_3), 1.02-1.07 (d, *J* = 6.7 Hz, 1 H, C(4a)H), 1.12-1.21 (m, 1 H, C(4)H), 1.31-1.39 (m, 1 H, C(8a)H), 1.47 (m, 1 H, C(8)H), 1.67-1.75 (m, 1 H, C(4)H), 1.80 (m, 1 H, C(9)H), 1.93 (dd, *J* = 13, 13 Hz, 1 H, C(5)H), 1.98-2.03 (m, 1 H, C(8)H), 2.16-2.29 (m, 2 H, C(5)H and C(7)H), 2.31-2.36 (m, 1 H, C(7)H), 2.41 (s, 3 H, $ArCH_3$), 3.17 (ddd, *J* = 14, 9.1, 4.7 Hz, 1 H, C(3)H), 3.33 (dd, *J* = 8.8, 4.9 Hz, 1 H, C(1)H), 3.64-3.72 (m, 1 H, C(3)H), 7.22 (d, *J* = 7.2 Hz, 2 H, ArH), 7.68 (d, *J* = 7.2 Hz, 2 H, ArH); ^{13}C NMR (126 MHz) δ 19.8 (q), 20.2 (q), 21.5 (q), 28.4 (t), 33.0 (y), 33.6 (t), 35.6 (d), 38.4 (t), 41.0 (t), 43.3 (d), 47.4 (t), 63.9 (d), 127.0 (d), 129.6, 138.1 (s), 143.2 (s), 209.2 (s).

20b: $[\alpha]^{23}_D$ +13.0° (*c* 0.20, $CHCl_3$); ^1H NMR (500 MHz) δ 0.86 (d, *J* = 6.7 Hz, 3 H, CH_3), 1.03 (d, *J* = 6.7 Hz, 3 H, CH_3), 1.24-1.30 (m, 1 H, C(4)H), 1.36 (qd, *J* = 13, 4.8 Hz, 1 H, C(4)H), 1.69-1.76 (m, 1 H, C(8)H), 1.85 (qd, *J* = 13, 4.8 Hz, 1 H, C(8)H), 2.03-2.14 (m, 2 H, C(5)H and C(9)H), 2.20-2.29 (m, 2 H, C(7)H and C(8a)H), 2.30-2.42 (m, 2 H, C(7)H and C(4a)H), 2.41 (s, 3 H, $ArCH_3$), 2.50 (m, 1 H, C(5)H), 2.86 (ddd, *J* = 14, 13, 3.2 Hz, 1 H, C(3)H), 3.56 (d, *J* = 11, 1 H, C(1)H), 3.68 (m, 1 H, C(3)H), 7.24 (d, *J* = 7.5 Hz, 2 H, ArH), 7.68 (d, *J* = 7.5 Hz, 2 H, ArH); ^{13}C NMR (126 MHz) δ 20.5 (q), 20.8 (q), 21.5 (q), 25.5 (t), 27.0 (t), 27.1 (d), 32.2 (d), 35.1 (d), 40.7 (t), 46.8 (t), 64.3 (t), 127.0 (d), 129.5 (d), 138.6 (s), 142.9 (s), 210.6 (s).

Acknowledgment. We wish to thank both the SC-NMR Laboratory of Okayama University and the FT-NMR Facilities in Faculty of Engineering, Okayama University for NMR experiments. We deeply appreciate K. Kushida (Varian Instruments, Japan) for 300-MHz NMR measurements and A. Kusai (JEOL, Japan) for exact mass determinations. The Crystallographic Research Center, Institute for Protein Research, Osaka University, is gratefully acknowledged for the X-ray reflection data collection.

Editor's Acknowledgment. We thank Dr. Robert Joyce of Sun City, FL, for his help in editing this manuscript.

Registry No. **3a**, 121731-69-9; **3b**, 121731-70-2; **4a**, 75197-06-7; **4b**, 121731-60-0; **5a**, 28875-17-4; **5b**, 58561-04-9; **6a**, 79069-50-4; **6b**, 79069-51-5; **7a**, 115378-33-1; **7b**, 115378-34-2; **8a**, 79069-13-9; **8b**, 79069-14-0; **9a**, 121731-61-1; **6b**, 121731-62-2; **10a**, 121731-63-3; **10b**, 121731-64-4; **11a**, 121731-65-5; **11b**, 121731-66-6; **12a**, 121731-67-7; **12b**, 121731-68-8; **13**, 121731-71-3; (±)-**17**, 121731-78-0; (±)-**18**, 121731-79-1; **19a**, 121731-74-6; **19b**, 121731-75-7; **19c**, 121731-76-8; **19d**, 121731-77-9; **20a**, 121731-80-4; **20b**, 121731-81-5; $EtO_2CCH{=}CH_2$, 140-88-5; $(i\text{-Pro})_2POCH_2COCH_3$, 67257-36-7; $CH_2{=}CHCH_2N(CO_2CH_3)(CH_2)_2CHO$, 121731-72-4; (*E*)-$CH_2{=}CHCH_2N(CO_2CH_3)(CH_2)_2CH{=}CHCOCH_3$, 121731-73-5.

Supplementary Material Available: Tables of atomic coordintes and equivalent isotropic thermal parameters, bond lengths and interbond angles, torsion angles, anisotropic thermal parameters of the non-H atoms, H-atom coordinates and isotropic thermal parameters, and bond lengths and interbond angles involving H-atoms and ORTEP view and stereoview (8 pages); listing of observed and calculated structure factor amplitudes (8 pages). Ordering information is given on any current masthead page.

The Facility of Formation of a Δ^6 Bond in Dihydromorphinone and Related Opiates

Hiroshi Nagase,[†] Akira Abe,[‡] and Philip S. Portoghese*,[†]

Department of Medicinal Chemistry, College of Pharmacy, University of Minnesota, Minneapolis, Minnesota 55455, and Toray Research Center, 1111 Tebiro Kamakura 248, Japan

Received February 22, 1989

Treatment of naltrexone, dihydromorphinone, or related opiates that contain a 6-keto group with acetic anhydride or *tert*-butyldimethylsilyl chloride under mild conditions afforded enol derivatives having a Δ^6 bond. Naltrexone also was found to undergo the Robinson annelation reaction with methyl vinyl ketone with facility and in high yield to give the β-hydroxy ketone **3**, whose stereochemistry was determined by means of 2D NMR spectroscopy. Upon acid treatment, **3** was dehydrated to the α,β-unsaturated ketone **4**. Acid-catalyzed equilibration of **4** afforded the unconjugated olefin **5**. These studies suggest that the Δ^6 bond is more stable than one that is exocyclic to ring C of the opiate because it permits ring flattening which may partially relieve torsional ring strain. The Δ^6 bond also may relieve an eclipsing interaction between a C-6 exocyclic substituent and the vicinal furan oxygen.

A number of studies on opiates that contain a C-6 carbonyl function have suggested that they can more readily be converted to enols or enolic derivatives than conventional ketones. For example, it has been reported that dihydromorphinone and related ketones are relatively resistant to addition by Grignard reagents and can form tertiary alcohols only with organolithium compounds.[1] Also, these opiates react more readily than normal ketones with hydrazine or with *N*-aminosuccinimide to afford pyrroles.[2] This reactivity profile and the fact that crystallographic studies[3,4] have shown ring C to be in a flatt-

[†] University of Minnesota.
[‡] Toray Research Center.

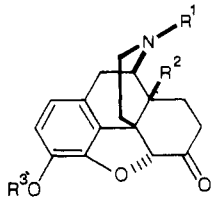
(1) Small, L.; Rapoport, H. *J. Org. Chem.* **1947**, *12*, 284.
(2) Lipkowski, A. W.; Nagase, H.; Portoghese, P. S. *Tetrahedron Lett.* **1986**, *27*, 4257.

0022-3263/89/1954-4120$01.50/0

ened chair conformation suggested that torsional ring strain and electronic factors may play a role in facilitating enol formation. In this paper we describe chemical studies that provide evidence for the greater stability of opiate products that contain a Δ^6 bond.

Chemistry

When naltrexone (**1a**) was maintained at 23 °C in excess acetic anhydride–pyridine for 2 days, the triacetate **2a** was

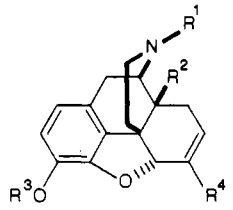


1

	R^1	R^2	R^3
a	$CH_2CH(CH_2)_2$	OH	H
b	$CH_2CH(CH_2)_2$	OH	$Si(Me)_2tBu$
c	CH_3	OH	H
d	CH_3	OH	$Si(Me)_2tBu$
e	CH_3	H	H
f	CH_3	H	$Si(Me)_2tBu$
g	$CH_2CH(CH_2)_2$	OAc	H
h	$CH_2CH(CH_2)_2$	OAc	$Si(Me)_2tBu$

obtained in high yield. The formation of the enol acetate under such mild conditions was surprising and has not been reported.

Similarly, exposure of a DMF solution of **1a** or its closely related ketones (**1c**, **1e**, **1g**) to 2 equiv of *tert*-butyldimethylsilyl chloride in the presence of imidazole afforded the disilyl ethers (**2b**, **2c**, **2d**, **2e**) in yields of 75–78%.



2

	R^1	R^2	R^3	R^4
a	$CH_2CH(CH_2)_2$	OAc	Ac	OAc
b	$CH_2CH(CH_2)_2$	OH	$Si(Me)_2tBu$	$OSi(Me)_2tBu$
c	CH_3	OH	$Si(Me)_2tBu$	$OSi(Me)_2tBu$
d	CH_3	H	$Si(Me)_2tBu$	$OSi(Me)_2tBu$
e	$CH_2CH(CH_2)_2$	OAc	$Si(Me)_2tBu$	$OSi(Me)_2tBu$
f	$CH_2CH(CH_2)_2$	H	H	OH

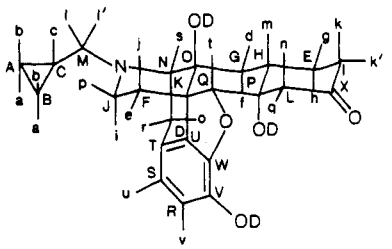
These silylation reactions were monitored by TLC. Relatively rapid silylation (<1 h) of the phenolic group afforded the monosilyl ethers (**1b**, **1d**, **1f**, **1h**), which were slowly (1–4 days) converted to the disilyl derivatives. The naltrexone monosilyl intermediate **1b** underwent conversion to **2b** in approximately half the time that was observed for its 14-acetate ester (**1h** → **2e**), whereas the oxymorphone intermediate **1d** was converted to **2c** about 4 times more rapidly than its hydromorphone analogue (**1f** → **2d**).

One possible explanation for this facilitation of the silylenolization reaction by the 14-hydroxyl group is that it may assist the removal of the axial C-7 proton. Also, the neighboring basic nitrogen may serve as an acceptor of the 14-hydroxyl proton to afford a more reactive nucleophile which would readily undergo acylation with acetic anhydride. This is supported by studies that have shown strong intramolecular hydrogen bonding between the basic nitrogen and the 14-hydroxyl proton of 14-hydroxycodeinone and its derivatives.[5] Our finding that oxymorphone (**1c**) is considerably less polar than hydromorphone (**1e**) (R_f = 0.48 and 0.18, respectively, $CHCl_3$–MeOH–NH_4OH, 50:4:0.4) provides additional support for intramolecular H bonding.

While the presence of the 14-hydroxyl group appears to contribute to enol formation, it does not appear to be the dominant factor that facilitates this process. That other factors are involved was suggested by our observation that opiate ketones without a 14-hydroxyl group [e.g., hydromorphone (**1e**)] still undergo silylenolization, while 2-methylcyclohexanone, propiophenone, and α-tetralone do not undergo this reaction under identical conditions.

In an effort to further investigate the facility of double-bond formation in ring C of the opiates, we subjected naltrexone (**1a**) to the Robinson annelation with methyl vinyl ketone. At 23 °C, the reaction proceeded smoothly in 1 N NaOH (aqueous methanol) to afford the annelation product **3** in 80% yield after 14 h. These reaction conditions are unusual in that generally the annelation of ketones requires strong base under anhydrous conditions.[6–10] The ease with which the product **3** was formed

Table I. Chemical Shifts for Compound 3[a]



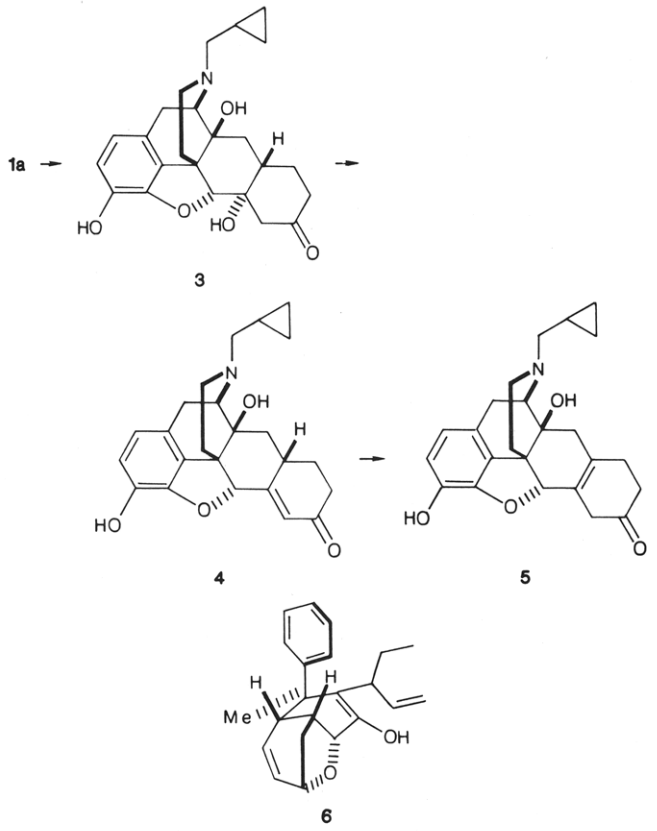
^{13}C	ppm	^1H	ppm
A	3.98	a	0.135
B	4.06	b	0.53
C	9.70	c	0.85
D	23.04	d	1.30
E	28.31	e	1.42
F	32.22	f	1.43
G	32.71	g	1.78
H	35.49	h	1.83
I	41.15	i	2.20
J	44.32	j	2.25
K	46.83	k, k'	2.34
L	53.76	l, l'	2.38
M	59.42	m	2.45
N	62.97	n	2.47
O	70.94	o	2.58
P	75.59	p	2.64
Q	93.19	q	2.76
R	118.25	r	3.01
S	119.07	s	3.07
T	124.47	t	4.36
U	131.52	u	6.52
V	137.77	v	6.69
W	144.73		
X	211.65		

[a] Determined at 100 MHz (^{13}C) and 400 MHz (^1H) and at 60 °C on 25 mg/mL in $CDCl_3$ after D_2O exchange of **3** (25 mg/mL).

(3) Sime, R. J.; Dobler, M.; Sime, R. L. *Acta Crystallogr.* **1976**, *B32*, 2937.
(4) Karle, I. L. *Acta Crystallogr.* **1974**, *B30*, 1682.
(5) Tada, H.; Kobayashi, M.; Sawa, Y. K. *Tetrahedron Lett.* **1969**, 1805.
(6) Bergmann, E. D.; Ginsburg, D.; Pappo, R. *Org. React. (N.Y.)* **1959**, *10*, 179.
(7) Odom, H. C.; Pinder, A. R.; Zalkow, L. H. *J. Chem. Soc. D* **1969**, 26.
(8) Marshall, J. A.; Ruden, R. A. *Tetrahedron Lett.* **1970**, 1239.

is consistent with facile enolate formation in **1a**.

The stereochemistry of the newly fused ring system in **3** was determined by means of NMR spectroscopy. In an effort to establish the relationship between ring juncture proton m and neighboring protons, we initially attempted to analyze the NMR spectrum at 40 °C. At this temperature, peak m overlapped with the signals for k and l, and g overlapped with h. However, measurement at 60 °C afforded separate peaks for these protons. All measurements therefore were carried out at 60 °C (Table I). These peaks were assigned carbons as methylenes, methines, or quaternary carbons by DEPT (distortionless enhancement by polarization transfer).[11-13] Further, ^1H–^{13}C COSY (correlated spectroscopy)[14] was employed to identify the ^1H nuclei directly attached to the individual ^{13}C nuclei, and long-range ^1H–^{13}C COSY also was used to establish the relationship between ^1H and ^{13}C with long-range coupling. Figure 1 illustrates the ^1H–^1H COSY[15,16] diagram whose results (Table I) confirm the skeletal structure of **3**.



With the above information and the studies described below, we were able to determine the stereochemistry of the new ring juncture. In this regard, our main focus was on the steric relationship of proton m with protons d, f, g, h, n, q, and t. The ring juncture proton m is coupled with protons f, d, h, and g, and the coupling constants are 12.0 Hz (m–f, trans), 2.6 Hz (m–d, cis), 12.0 Hz (m–h, trans), and 4.8 Hz (m–g, cis), respectively. The steric

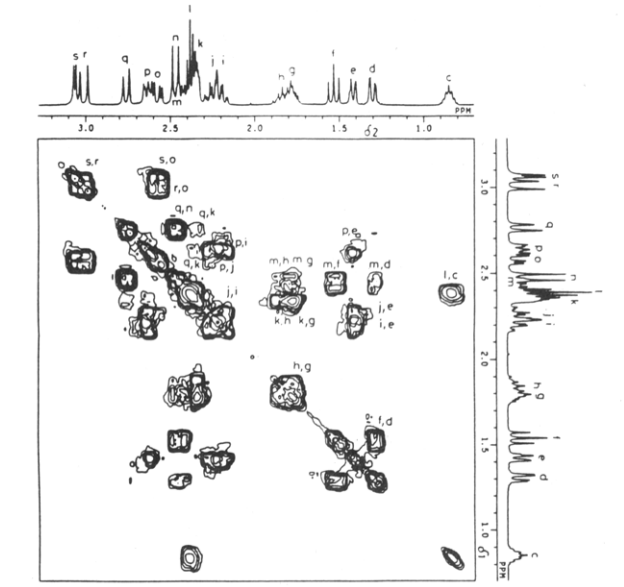


Figure 1. Proton COSY of **3**.

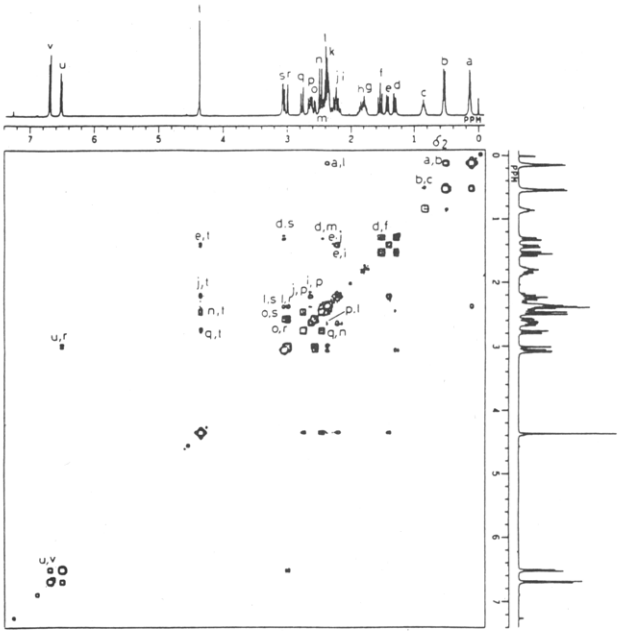


Figure 2. NOE 2D NMR of **3**.

relationship between t and m was established from the NOE correlated 2D NMR spectra[17] (Figure 2), and the NOE difference spectra[18] (Figure 3) were carried out so as to clarify the relationship of proton t with protons d, f, g, h, m, n, and q. There are many correlations in Figure 2, which are useful for elucidating the three-dimensional structure. For example, e–t, j–t, q–t, and n–t (m and n are overlapping and cannot be distinguished by this method) show the close proximity of the protons e, j, n (m), and q to the methine proton t. Since separation of the overlapping peaks m and n was accomplished in 25 mM $CDCl_3$ solution, the NOE difference spectra were determined under these conditions (Figure 3a). On irradiation of methine proton t, a NOE was observed for protons e, j, m, n, and q (Figure 3b). Moreover, irradiation of the methine proton m afforded a NOE on protons t, g, and d (Figure 3c). It was not possible to measure the NOE on proton

(9) Coates, R. M.; Shaw, J. E. *J. Am. Chem. Soc.* **1970**, *92*, 5657.
(10) Scanio, C. J. V.; Starrett, R. M. *J. Am. Chem. Soc.* **1971**, *93*, 1539.
(11) Doddrell, D. M.; Pegg, D. T.; Bendall, M. R. *J. Magn. Reson.* **1982**, *48*, 323.
(12) Bendall, M. R.; Pegg, D. T. *J. Magn. Reson.* **1983**, *53*, 272.
(13) Sprensen, O. W.; Ernst, R. R. *J. Magn. Reson.* **1982**, *51*, 477.
(14) Freeman, R.; Morris, G. A. *J. Chem. Soc., Chem. Commun.* **1978**, 64.
(15) Aue, W. P.; Barthold, E.; Ernst, R. R. *J. Chem. Phys.* **1976**, *64*, 2229.
(16) Bax, A.; Freeman, R. *J. Magn. Reson.* **1981**, *44*, 542.
(17) Macura, S.; Ernst, R. R. *Mol. Phys.* **1980**, *41*, 95.
(18) Sanders, J. K.; Mersh, J. D. *Prog. Nucl. Magn. Reson.* **1983**, *15*, 353.

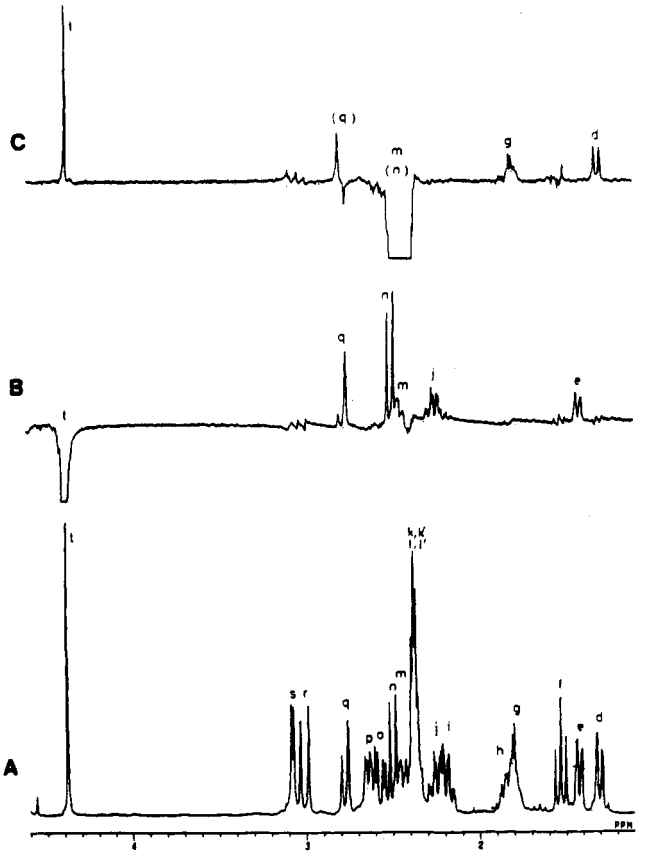


Figure 3. Comparison of the 400-MHz NMR spectrum of **3** in $CDCl_3$ (A) with its NOE difference spectrum on irradiation of proton t (B) and irradiation of proton m (C).

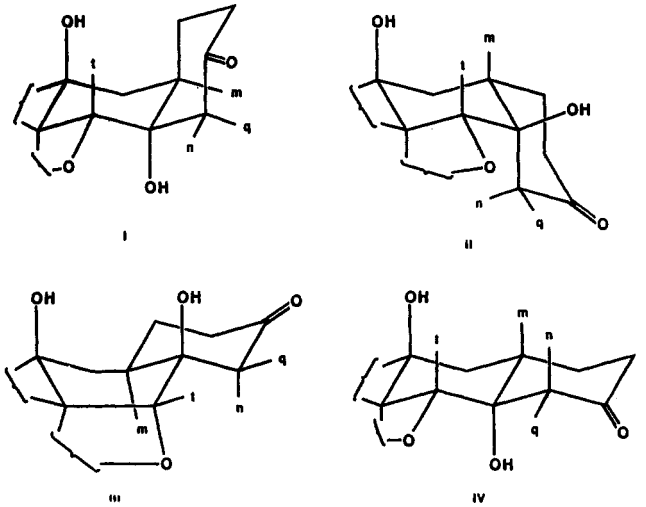


Figure 4. Possible ring junctures for annelation product **3**.

n upon irradiation of m because of the proximity of chemical shifts of these protons.

Of the four possible new ring junctures (I–IV, Figure 4), only structure IV is consistent with the NMR data. The NOE between t and m rules out I and III because these protons are on opposite sides of ring C. Structure II is eliminated on the basis that it would be expected that J_{mh} should be small (<5 Hz) if this were the case. This leaves the remaining structure IV, which is consistent with both the NOE and the coupling constants between m and vicinal protons d, f, g, and h. With regard to the latter, J_{mh} and J_{mf} are both 12 Hz, which is consistent with transdiaxial coupling; J_{mg} and J_{md} are relatively small (2.6 and 4.8 Hz) and in harmony with axial-equatorial coupling.

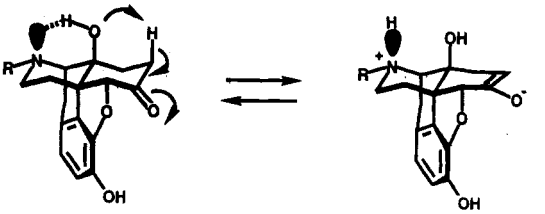


Figure 5. Anchimeric assistance in enolization.

When a solution of **3** in a mixture of 1 N HCl and methanol (2:3) was allowed to stand at 23 °C for 9 days, the α,β-unsaturated ketone **4** was obtained in 65% yield. Refluxing a solution of **4** in a mixture of glacial acetic acid and water (2:1) for 48 h afforded the unconjugated ketone **5** (70%).

Discussion

The facility with which the ketone moiety of compounds in series **1** can be enolized was suggested by reaction with acetic anhydride–pyridine or with *tert*-butyldimethylsilyl chloride. In both cases the corresponding enol derivatives (series **2**) were formed in high yield at room temperature, while under identical conditions neither propiophenone nor α-tetralone formed the enol derivatives.

The fact that the 14-hydroxyl group facilitates enolization suggests that it may accomplish this by assisting in the abstraction of the axial C-7 proton. It is possible that anchimeric assistance by the basic nitrogen might facilitate this process (Figure 5). Also, such anchimeric assistance may in part account for the facile esterification of the 14-hydroxyl group. However, the fact that the 14-deoxy opiate **1e** appears to have a greater tendency to enolize than normal ketones suggests that additional factors are involved in facilitating enol formation.

Further evidence for the greater-than-normal enolic character of the 6-keto group was obtained from the unusually facile Robinson annelation reaction of naltrexone (**1a**) with methyl vinyl ketone to afford the expected product **3** in high yield. The facility of this conversion can be rationalized on the basis that the enol form of naltrexone **2f** is more readily deprotonated by base to form the enolate than the corresponding ketone species of naltrexone (**1a**).

The fact that the annelation product **3** was dehydrated under mild conditions to the α,β-unsaturated ketone **4** as the sole product, which was isomerized to the β,γ-unsaturated ketone **5** under more forcing conditions, suggests that formation of the conjugated ketone **4** is kinetically controlled and that the unconjugated ketone **5** is thermodynamically more stable. This relationship is opposite to what is generally observed, as resonance stabilization through conjugation usually confers greater stability to α,β-unsaturated ketones.[19] These results are consistent with the other evidence that suggests greater enolic character for naltrexone and related ketones when compared to normal ketones. It appears that this may be related to the favorable presence of a Δ^6 bond in ring C.

What is the origin of the stability conferred by a double bond in this opiate system? A recent report[20] on the isolation of a stable, simple enol **6** may be relevant to this question, as it appears to share some features with the opiate enol **2f**. The enhanced stability of the enol **6** was attributed in part to the relief of unfavorable dipolar interactions between the carbonyl and the nearly eclipsed

(19) House, H. O.; Trost, B. M.; Magin, R. W.; Carlson, R. G.; Franck, R. W.; Rasmusson, G. H. *J. Org. Chem.* **1965**, *30*, 2513.
(20) Pratt, D. V.; Hopkins, P. B. *J. Am. Chem. Soc.* **1987**, *109*, 5553.

ether bridge. It is conceivable that a similar mechanism may promote enol formation in the opiate series **1**, as it can be seen that the keto group and the furan ether oxygen are nearly eclipsed in the ketone, but not in the enol (Figure 5). Enolization would relieve dipolar destabilization by the flattening of ring C. Such flattening also may reduce torsional strain in ring C. Similarly, the greater stability of the unconjugated enone **5** over its conjugated isomer **4** may be due to ring C flattening and this would also relieve eclipsing of the exocyclic double bond with the vicinal furan oxygen.

Experimental Section

Melting points were determined in open capillary tubes on a Thomas-Hoover apparatus and are uncorrected. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. IR spectra were obtained on a Perkin-Elmer 281 infrared spectrophotometer. NMR spectra were recorded at ambient temperature on IBM-Bruker AC-300 using $CDCl_3$ as solvent and Me_4Si as internal standard. 2D NMR spectra were determined in $CDCl_3$ by using a JEOL JNM-GX400 apparatus at Toray Research Center, 1111 Tebiro Kamakura 248, Japan. Mass spectra were obtained on an AEI MS 30, Finnigan 4000 CI, and VG 70, 70 EHF instrument. All TLC data were obtained with Merck 5715 silica gel by using $CHCl_3$–MeOH–NH_4OH (CMA) or $CHCl_3$–MeOH (CM) solvent systems. Unless otherwise stated, all reagents and solvents were reagent grade and used without subsequent purification.

3-[(*tert*-Butyldimethylsilyl)oxy]-17-(cyclopropylmethyl)-4,5α-epoxy-14-hydroxymorphinan-6-one (1b). To a solution of naltrexone hydrochloride (**1a**·HCl) (2.00 g, 5.3 mmol) in DMF (6 mL) were added imidazole (2.00 g, 29.4 mmol) and *tert*-butyldimethylsilyl chloride (2.00 g, 13.2 mmol). The resulting solution was stirred at 23 °C for 40 min. To the mixture were added water and ether, and the mixture was extracted with ether (3×). The combined organic phases were washed with water, dried ($MgSO_4$), and concentrated to give a solid, which was recrystallized from EtOH to yield pure monosilyl ether **1b** (2.12 g, 88%), R_f = 0.43 (CMA, 50:1:0.1), mp 94–95 °C: IR (KBr, cm^{-1}) 3370 (14-OH), 1725 (6-C=O); ^1H NMR ($CDCl_3$) δ 0.20 (s, 3 H, SiMe), 0.28 (s, 3 H, SiMe), 1.00 (s, 9 H, SiCMe), 4.61 (s, 1 H, 5-H); MS (EI), *m/e* 455 (M^+). Anal. Calcd for $C_{28}H_{37}O_4NSi$: C, 68.75; H, 8.02; N, 3.08. Found: C, 68.69; H, 7.92; N, 3.33.

3-[(*tert*-Butyldimethylsilyl)oxy]-4,5α-epoxy-14-hydroxy-17-methylmorphinan-6-one (1d). A solution of oxymorphone hydrochloride (**1c**·HCl) (150 mg, 0.44 mmol) was treated in DMF as described for the preparation of **1b** to afford the monosilyl ether **1d** (130 mg, 71%), R_f = 0.28 (CMA, 50:1:0.1), mp 140–141 °C: IR and NMR characteristics similar to those described for **1b**; MS (EI), *m/e* 415 (M^+). Anal. Calcd for $C_{23}H_{33}O_4NSi$: C, 66.46; H, 8.00; N, 3.37. Found: C, 66.41; H, 8.08; N, 3.39.

3-[(*tert*-Butyldimethylsilyl)oxy]-4,5α-epoxy-17-methylmorphinan-6-one (1f). A solution of hydromorphone hydrochloride (**1e**·HCl) (150 mg, 0.44 mmol) in DMF was treated as described for **1b** to afford crude product **1f**. Preparative TLC (silica gel, 5% MeOH–$CHCl_3$) yielded pure monosilyl ether **1f** (120 mg, 75%), R_f = 0.34 (CMA, 50:4:0.1): IR (KBr); IR and NMR spectral characteristics similar to those of **1b**; high-resolution MS (EI), *m/e* 399.2265 (calcd for $C_{23}H_{33}O_3NSi$ (399.2229).

14-Acetoxy-17-(cyclopropylmethyl)-4,5α-epoxy-3-hydroxymorphinan-6-one (1g). A solution of naltrexone (**1a**) (500 mg, 1.47 mmol) in Ac_2O (20 mL) was stirred under reflux for 1 h. The Ac_2O was removed in vacuo, and the residue was dissolved in 10% aqueous H_2SO_4 (20 mL). The resulting solution was allowed to stand at 23 °C for 20 h and then basified (pH 8) with 10% NH_4OH. The mixture was extracted with $CHCl_3$ (3×), and the combined organic phases were washed with brine, dried, and concentrated to give crude product (550 mg), which was recrystallized from MeOH to yield pure acetate **1g** (350 mg, 62%), mp 205–207 °C: IR (KBr, cm^{-1}) 1735 (br, OAc and ketone); ^1H NMR ($CDCl_3$) δ 2.21 (s, 3 H, OAc); MS (EI), *m/e* 383 (M^+). Anal. Calcd for $C_{22}H_{25}O_5N$: C, 68.93; H, 6.53; N, 3.66. Found: C, 68.81; H, 6.65; N, 3.57.

14-Acetoxy-3-[(*tert*-butyldimethylsilyl)oxy]-17-(cyclopropylmethyl)-4,5α-epoxymorphinan-6-one (1h). To a solution of **1g**·HCl (100 mg, 0.26 mmol) and imidazole (70 mg, 1.03 mmol) in DMF (1 mL) was added *tert*-butyldimethylsilyl chloride (78 mg, 0.52 mmol). The resulting mixture was allowed to stand at 23 °C for 1 h, water was then added, and the mixture was extracted with ether (3×). The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated to give a crude product, which was recrystallized from EtOH to afford pure monosilyl ether **1h** (80 mg, 89%), R_f = 0.70 (CM, 100:2.5), mp 130–131 °C: IR (KBr, cm^{-1}) 1735 (ester, C=O); ^1H NMR ($CDCl_3$) δ 0.19 (s, 3 H, SiMe), 0.27 (s, 3 H, SiMe), 1.00 (s, 9 H, SiCMe), 2.20 (s, 3 H, OAc); MS (EI), *m/e* 497 (M^+). Anal. Calcd for $C_{28}H_{39}O_5NSi$: C, 67.57; H, 7.90; N, 2.81. Found: C, 67.43; H, 7.94; N, 2.89.

3,6,14-Triacetoxy-17-(cyclopropylmethyl)-6,7-didehydro-4,5α-epoxymorphinan (2a). A solution of naltrexone (**1a**) (500 mg, 1.47 mmol) in pyridine (10 mL) and Ac_2O (20 mL) was allowed to stand at 23 °C for 2 days. The solution was concentrated in vacuo to give the triacetate **2a** (690 mg, 100%): IR (liquid film, cm^{-1}) 1768, 1736 (acetate); high-resolution MS (EI), *m/e* 467.1965 (calcd for $C_{26}H_{29}O_7N$ 467.1989).

17-(Cyclopropylmethyl)-3,6-bis[(*tert*-butyldimethylsilyl)oxy]-6,7-didehydro-4,5α-epoxy-14-hydroxymorphinan (2b). To a stirred solution of naltrexone hydrochloride (**1a**·HCl) (2.00 g, 5.3 mmol) and imidazole (2.0 g, 29 mmol) in DMF (6 mL) was added *tert*-butyldimethylsilyl chloride (2.00 g, 13.2 mmol). The solution was stirred at 23 °C for 23 h, and then water was added. The resulting mixture was extracted with ether (3×), and the combined organic phases were washed with brine, dried, and concentrated to give the crude product **2b**. The product was recrystallized from EtOH to afford the pure silyl enol ether **2b** (2.5 g, 75%), R_f = 0.67 (CMA, 50:1:0.1), mp 93–94 °C: IR (KBr, cm^{-1}) 3350 (14-OH), 1672 (double bond); ^1H NMR ($CDCl_3$) δ 0.15 (s, 3 H, SiMe), 0.17 (s, 3 H, SiMe), 1.01 (s, 3 H, SiMe), 1.14 (s, 3 H, SiMe), 0.93 (s, 9 H, SiCMe), 0.96 (s, 9 H, SiCMe), 4.91 (dd, 1 H, J = 5.7 Hz, 2.7 Hz, 7-H); MS (EI), *m/e* 569 (M^+). Anal. Calcd for $C_{32}H_{51}O_4NSi_2$: C, 67.49; H, 8.96; N, 2.46. Found: C, 67.21; H, 8.75; N, 2.37.

3,6-Bis[(*tert*-butyldimethylsilyl)oxy]-6,7-didehydro-4,5α-epoxy-14-hydroxy-17-methylmorphinan (2c). A stirred solution of oxymorphone (**1c**) (100 mg, 0.33 mmol) was treated in DMF (2 mL) as described for the preparation of **2b** to afford pure enol ether **2c** (132 mg, 75%), R_f = 0.58 (CMA, 50:1:0.1), mp 138–140 °C: IR (KBr, cm^{-1}) 3350 (14-OH), 1667 (double bond); ^1H NMR ($CDCl_3$) δ 0.10 (s, 3 H, SiMe), 0.15 (s, 3 H, SiMe), 0.17 (s, 3 H, SiMe), 0.18 (s, 3 H, SiMe), 0.93 (s, 9 H, SiCMe), 4.90 (dd, 1 H, J = 5.6 Hz, 2.6 Hz, 7-H); MS (EI), *m/e* 529 (M^+). Anal. Calcd for $C_{29}H_{47}O_4NSi_2$: C, 65.76; H, 8.88; N, 2.64. Found: C, 65.77; H, 8.75; N, 2.63.

3,6-Bis[(*tert*-butyldimethylsilyl)oxy]-6,7-didehydro-4,5α-epoxy-17-methylmorphinan (2d). A stirred solution of hydromorphone (**1e**) (100 mg, 0.35 mmol) was treated in DMF (2 mL) as described for the preparation of **2b** except that the mixture was stirred at 23 °C for 4 days. The product was recrystallized from EtOH with Et_3N to yield pure enol ether **2d** (100 mg, 78%), R_f = 0.54 (CMA, 50:4:0.1), mp 93–94 °C: IR (KBr, cm^{-1}) 1658 (double bond); ^1H NMR ($CDCl_3$) δ 0.07 (s, 3 H, SiMe), 0.13 (s, 3 H, SiMe), 0.15 (s, 3 H, SiMe), 0.17 (s, 3 H, SiMe), 0.92 (s, 9 H, SiCMe), 0.96 (s, 9 H, SiCMe), 4.93 (dd, 1 H, J = 6.5 Hz, 1.7 Hz, 7-H); high-resolution MS (EI), *m/e* 513.3068 (calcd for $C_{29}H_{47}O_3NSi_2$ 513.3095).

14-Acetoxy-3,6-bis[(*tert*-butyldimethylsilyl)oxy]-17-(cyclopropylmethyl)-6,7-didehydro-4,5α-epoxymorphinan (2e). To a stirred solution of **1g** (105 mg, 0.27 mmol) and imidazole (168 mg, 2.48 mmol) in DMF (2 mL) was added *tert*-butyldimethylsilyl chloride (186 mg, 1.24 mmol). The mixture was stirred at 23 °C for 35 h and worked up as described for **2d**. The product was recrystallized from EtOH to give pure enol ether **2e** (120 mg, 77%), R_f = 0.84 (CM, 100:2.5), mp 141–143 °C: IR (KBr, cm^{-1}) 1723 (OAc), 1669 (double bond); ^1H NMR ($CDCl_3$) δ 0.11 (s, 3 H, SiMe), 0.15 (s, 3 H, SiMe), 0.16 (s, 3 H, SiMe), 0.18 (s, 3 H, SiMe), 0.95 (s, 9 H, SiCMe), 0.97 (s, 9 H, SiCMe), 2.08 (s, 3 H, OAc), 4.80 (dd, J = 6.6 Hz, 1.9 Hz, 7-H); MS (EI), *m/e* 612 (M^+). Anal. Calcd for $C_{34}H_{53}O_5NSi_2$: C, 66.75; H, 8.67; N, 2.30. Found: C, 66.86, H, 8.52; N, 2.35.

[8*R*-(4b*R,8α,8aβ,9aβ,13aα,13bβ)]-7-(Cyclopropylmethyl)-6,7,8,8a,9,9a,10,11,13a,13b-decahydro-1,8a,13a-trihydroxy-4,8-methano-5*H*-benzo[*g*]benzofuro[3,2-*e*]iso-**

quinolin-12(13*H*)-one (3). To a solution of naltrexone hydrochloride (2 g, 5.3 mmol) and 1 N NaOH (20 mL, 20 mmol) in MeOH (40 mL) was added methyl vinyl ketone (1 mL, 12.3 mmol) in an ice bath. After the mixture was stirred at room temperature for 14 h under nitrogen, additional methyl vinyl ketone (0.3 mL, 3.7 mmol) was added. The mixture was stirred for 2 h and then neutralized with 10% HCl and 1 N HCl. The resulting mixture was concentrated and extracted with $CHCl_3$ (3×). The combined chloroform extracts were washed with brine and dried, and the solvent was removed to give a crude product, which was purified on a Sephadex column (LH-20, MeOH) to afford a solid, which was recrystallized from AcOEt to yield pure **3** (1.68 g, 80%), mp 252–254 °C: IR (KBr, cm^{-1}) 3400 (OH), 1718 (ketone); ^1H NMR ($CDCl_3$) (see Table I); MS (EI), *m/e* 411 (M^+). Anal. Calcd for $C_{24}H_{29}O_5N$: C, 70.07; H, 7.06; N, 3.41. Found: C, 69.88; H, 7.22; N, 3.45.

[8*R*-(4b*R,8α,8aβ,9aβ,13bβ)]-7-(Cyclopropylmethyl)-6,7,8,8a,9,9a,10,11-octahydro-1,8a-dihydroxy-4,8-methano-5*H*-benzo[*g*]benzofuro[3,2-*e*]isoquinolin-12(13b*H*)-one (4).** A solution of **3** (210 mg, 0.51 mmol) in a mixture of 1 N HCl (2 mL) and MeOH (3 mL) was allowed to stand at 23 °C for 9 days. The solution was neutralized with 1 N NaOH, concentrated, and extracted with $CHCl_3$ (3×). The combined chloroform extracts were washed with brine and dried, and the solvent was removed to give a crude product, which was recrystallized from $CHCl_3$ to afford the α,β-unsaturated ketone **4** (130 mg, 65%), mp 230 °C dec: IR (KBr, cm^{-1}) 3400 (OH), 1675 (conjugated ketone), 1616 (double bond); ^1H NMR ($CDCl_3$) δ 5.05 (s, 1 H, 5-H), 6.50 (d, 1 H, *J* = 2.4 Hz, 21-H vinyl); MS (FAB) 393 (M^+). Anal. Calcd for $C_{24}H_{27}O_4N \cdot 0.2CHCl_3 \cdot 2.4H_2O$: C, 62.60; H, 6.43; N, 3.04. Found: C, 62.60; H, 6.74; N, 3.20.

[8*R*-(4b*R,8α,8aβ,13bβ)]-7-(Cyclopropylmethyl)-6,7,8,8a,9,10,11,13b-octahydro-1,8a-dihydroxy-4,8-methano-5*H*-benzo[*g*]benzofuro[3,2-*e*]isoquinolin-12(13*H*)-one (5).** A solution of **4** (135 mg, 0.30 mmol) in a mixture of AcOH (6 mL) and water (3 mL) was stirred under reflux for 48 h. After concentration of the solution, $CHCl_3$ was added and the mixture was neutralized with saturated $NaHCO_3$ and separated. The aqueous phase was extracted with $CHCl_3$ (3×). The combined organic phases were washed with brine and dried, and the solvent was removed to give a crude product. The product was purified by preparative TLC (silica gel, 7% MeOH in saturated NH_4OH–$CHCl_3$) to afford pure unconjugated ketone **5** (90 mg, 70%): IR (KBr, cm^{-1}) 3400 (OH), 1700 (unconjugated ketone); high-resolution MS (EI), *m/e* 393.1945 (calcd for $C_{24}H_{27}O_4N$ 393.1952).

Acknowledgment. This work was supported by the National Institute on Drug Abuse.

Photocycloaddition of 4,5′,8-Trimethylpsoralen and Oleic Acid Methyl Ester: Product Structures and Reaction Mechanism†

Kathleen G. Specht,‡,∥ W. Robert Midden,*,§ and Miles R. Chedekel‡,⊥

The Center for Photochemical Sciences, Department of Chemistry, Bowling Green State University, Bowling Green, Ohio 43403, and Division of Environmental Chemistry, School of Hygiene and Public Health, The Johns Hopkins University, Baltimore, Maryland 21205

Received February 14, 1989

The stereochemical structures of the four adducts formed between oleic acid methyl ester (OAME) and 4,5′,8-trimethylpsoralen (tmPso) have been determined. Assignment of the tmPso ^1H NMR spectrum was accomplished by analogy to two coumarin model compounds and with the use of homonuclear decoupling and resonance enhancement. Assignment of the ^1H NMR spectra for the OAME–tmPso adducts was made by analogy to the spectra of OAME and tmPso and using 2D *J*-resolved and COSY analyses. The configurations of the cyclobutyl rings in these adducts was determined by MM2 energy minimization calculations, homonuclear ^1H NOE analysis, and comparison of products obtained with *cis*-OAME and *trans*-EAME (elaidic acid methyl ester). Only four of the eight possible disastereomeric adducts are detected. These adducts have the cis-cis-HH, cis-cis-HT, trans-cis-HH, and trans-cis-HT configurations. The lack of formation of the other isomers may be due to the geometric requirements of exciplex formation. The mechanism of the reaction was established to involve initial bond formation at the 4 position of tmPso, most likely to form a diradical intermediate. The rate of dissociation of the trans diradical is much faster than ring closure, in contrast to the cis diradical whose rate of ring closure is at least as fast as dissociation. The rate of cis–trans isomerization of the 9,10-bond of the fatty ester portion of the diradical is faster than ring closure for the cis diradical and slower than ring closure for the trans diradical.

Introduction

Psoralens, the linear members of the furocoumarin family, are some of the most effective agents available for the photochemotherapy of a number of skin diseases such as psoriasis and vitiligo.[1] The therapeutic benefit of this treatment is thought to be due to the inhibition of hyperproliferation of the skin keratinocytes. The use of psoralens is limited due to their carcinogenicity.[2] The chemical mechanisms of psoralens have been studied for almost 20 years with the hope that a way could be found to eliminate psoralen carcinogenicity while retaining the beneficial antiproliferative effect.

Psoralens photochemically add to the 5,6-bond of pyrimidines in DNA, forming cyclobutyl-linked adducts.[3-7]

* To whom correspondence should be addressed.
‡ The John Hopkins University.
§ Bowling Green State University.
∥ Current address: Center for Photochemical Sciences, Department of Chemistry, Bowling Green State University, Bowling Green, OH 43403.
⊥ Current address: Advanced Polymer Systems, 3696 Haven St., Redwood City, CA 94063.

† Abbreviations. OAME: *cis*-oleic acid methyl ester. EAME: *trans*-elaidic acid methyl ester. tmPso: 4,5′,8-trimethylpsoralen. 8-MOP: 8-methoxypsoralen. DMC: 4,8-dimethyl-7-methoxycoumarin. DAC: 4,8-dimethyl-7-acetoxycoumarin. PUVA: psoralen plus UVA.

(1) Fitzpatrick, T. B.; Pathak, M. A. *National Cancer Institute Monograph 66*, **1984**, 3–11.
(2) Roelandts, R. *Arch. Dermatol.* **1984**, *120*, 662–669.
(3) Song, P. S.; Tapley, K. J., Jr. *Photochem. Photobiol.* **1979**, *29*, 1177–1197.
(4) Parsons, B. J. *Photochem. Photobiol.* **1980**, *32*, 813–821.

0022-3263/89/1954-4125$01.50/0