

Enantioselective Photochemical Reactions of *N*-Phenyl Enaminones in Inclusion Complex Crystals Using a Chiral Host Compound

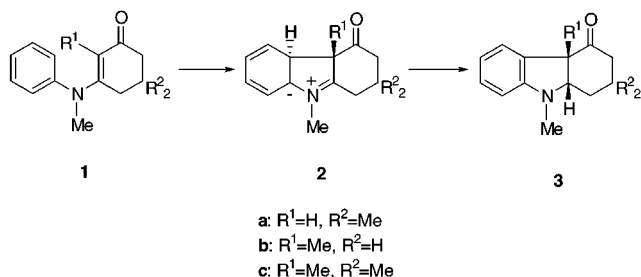
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Received September 30, 1998

Enantioselective reaction of *N*-methyl-*N*-phenyl-3-amino-2-cyclohexen-1-one derivatives to the corresponding *N*-methylhexahydro-4-carbazolones has been accomplished by photolysis in a water suspension of 1:1 inclusion compounds of the starting material with optically active host compounds derived from tartaric acid. 3-(*N*-Methylanilino)-2,5,5-trimethyl-2-cyclohexen-1-one formed two kinds of dimorphous crystals, and one of these gave an optically active carbazolonone derivative by photolysis, but the other one was photochemically inert. X-ray structure analysis showed that two reaction centers, the phenyl and cyclohexenone groups of the reactant, are located in close and distant positions respectively in these two inclusion compounds.

Photoreaction of *N*-phenyl enaminones such as the *N*-methyl-*N*-phenyl-3-amino-2-cyclohexen-1-one derivatives (**1**) to the corresponding *N*-methylhexahydro-4-carbazolones (**3**) via the dipolar ionic intermediate (**2**) produced by a conrotatory ring closure has been reported.¹ This photocyclization reaction has received the attention of several research groups^{2–4} since **3** is a useful synthon for building interesting heterocyclic compounds such as indole alkaloids.^{2,3}



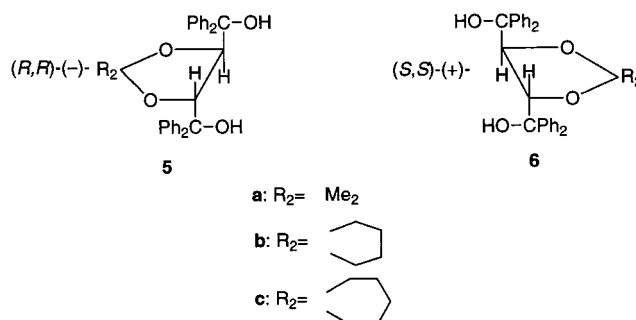
To use **3** as a synthon, it is desirable that it be optically pure. We sought to carry out the photoconversion of **1** to **3** enantioselectively and found that irradiation of inclusion compounds of **1** with the chiral host compounds **5** or **6** in the solid state does indeed give optically active **3**. We also found that inclusion complexation of **5c** and **1a** gave two dimorphous inclusion crystals as colorless prisms (**7cap**) and needles (**7can**), which upon photolysis

Table 1. Physical Data of 1:1 Host:Guest Inclusion Compounds **7 of Host **5** with Guest **1** Prepared by Recrystallization**

host	guest	inclusion compound	
		crystal morphology ^a	mp (°C)
5a	1a	7aa	prisms 114–116
5b	1a	7ba	needles 136–138
5c	1a	7cap	prisms 146–148
5c	1a	7can	needles 148–150
5a	1b	7ab	needles 133–135
5b	1b	7bb	needles 141–145
5c	1b	7cb	prisms 122–129

^a All crystals are colorless.

gave **3a** of 87% ee and recovered unchanged **7can**, respectively. X-ray analysis showed that the phenyl and cyclohexenone moieties of the **1a** molecule are arranged in close proximity in **7cap** but are remote in **7can**, despite **1a** molecules being arranged in a chiral form in both **7cap** and **7can**.



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Recrystallization of **5** and **1** from solvent gave 1:1 inclusion compounds with the crystal morphology and melting point data summarized in Table 1. However, **1c** does not form an inclusion complex with **5** by this method. Although recrystallization of **5c** and **1a** gave a mixture of **7cap** and **7can**, if one piece of seed crystal of

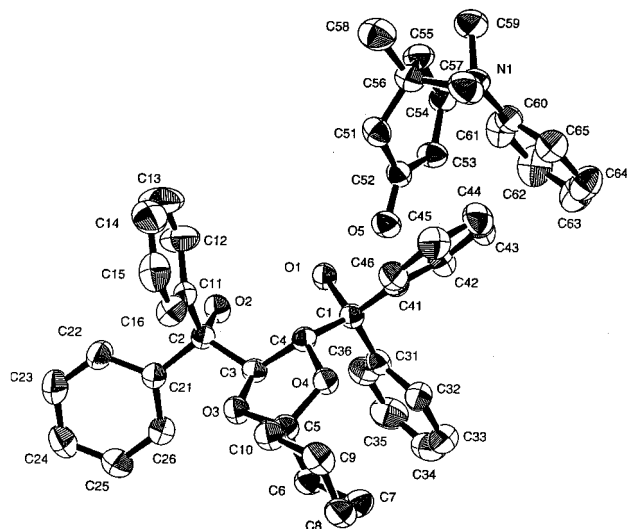
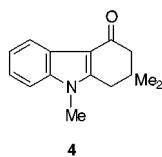


Figure 1. ORTEP drawing of the crystal structure of **7cap**.

Table 2. Photoreaction of 7 Prepared by Recrystallization

inclusion compound	irradiation time (h)	product			
		conv (%)	yield (%)	optical purity (% ee)	
7aa	16	(+)- 3a ^a	29	6	97
7ba	100	no reaction occurred			
7cap	11.5	(+)- 3a ^b	9	54	87
7can	100	no reaction occurred			
7ab	23	(-)- 3b	86	43	94
7bb	13	(-)- 3b	64	20	85
7cb	12	(-)- 3b	46	26	62

^a **4** was obtained in 16% yield. ^b **4** was obtained in 3% yield.



7cap is added during the recrystallization, then **7cap** crystals can be obtained in large quantity.

Irradiation of powdered **7** as a water suspension gave the optically active photocyclization product **3**. For example, irradiation of the inclusion compound **7aa** gave (+)-**3a** of 97% ee. Starting material **1a** in the inclusion compound was converted into its photoreaction products in 29% yield. (+)-**3a** and the dehydrogenated compound **4** of its photoreaction products were obtained in 6 and 16% yield, respectively. Conversion, chemical, and optical yields of the reactions are summarized in Table 2. The enantiomeric excess of **3** did not change with the degree of conversion. In the cases of **7aa** and **7cap**, the dehydrogenated compound **4** was obtained as a byproduct. **7ba** and **7can** are photochemically inert. To know the reason for this inertness, the X-ray structures of **7can** and **7cap** were analyzed and compared.⁵ In **7cap**, its two reaction centers, the carbon atom, C53, of the cyclohexenone group and the carbon atom, C61 or C65, of the phenyl group, are in close contact as shown in Figure 1. The distances C53...C61 and C53...C65 are 3.769(6) and 3.161(4) Å, respectively. In **7can**, on the other hand,

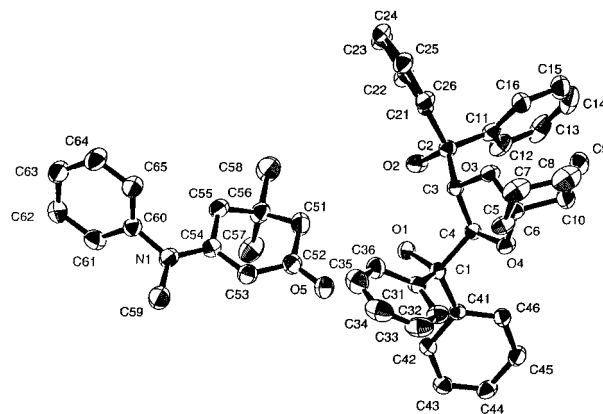
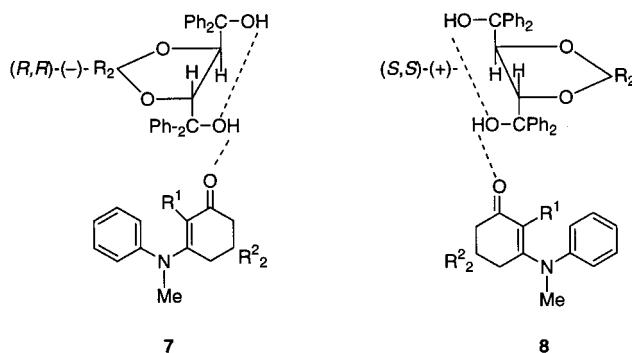


Figure 2. ORTEP drawing of the crystal structure of **7can**.

those two atoms are too distant to permit reaction, because the phenyl groups are rotated around the N1–C54 bond by about 180° (Figure 2). In **7ba**, the **1a** molecules are probably arranged also in an unfavorable conformation for reaction.

The chiral arrangement of **1a** molecules in the inclusion crystals **7cap** and **7can** was proven by X-ray analysis. CD spectral measurement in the solid state,⁶ however, can detect the chiral arrangement of **1** in **7** more simply and easily. For example, **7cap** showed a CD spectrum with (+)-Cotton effect in Nujol mull (Figure 3).⁶ On the other hand, the inclusion compound of **6c** and **1a** (**8cap**) showed a CD spectrum with (–)-Cotton effect (Figure 3). These two spectra are in a nice mirror-imaged relation. Similarly, **7can** and **8can** showed CD spectra with a mirror-imaged relation (Figure 4). These CD spectra are attributed to a chiral arrangement of **1a**, because **5** and **6** themselves which have no chromophore do not show a CD spectrum in these regions.



Host–guest inclusion complexes can be prepared by recrystallization of the components from a solvent. In some cases, the inclusion complex is not formed by this method. However, we found that, even in such cases, mixing of powdered host and guest compounds in the absence of solvent can give inclusion crystals.⁷ For example, mixing of **5a** and **1c** for 1 h at room temperature using a planetary micro mill gave the 1:1 inclusion complex (**7ac**), and its photoreaction gave (+)-**3c** of 59% ee (64% conversion, 23% yield). Irradiation in a water

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(5) The crystal structure analysis of **7cap** and **7can** will be published elsewhere.

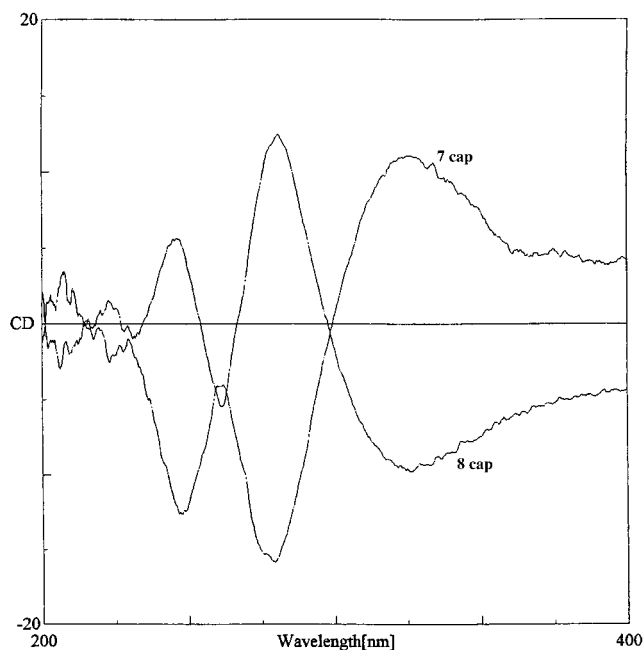


Figure 3. CD spectra of **7cap** and **8cap** in Nujol mull.

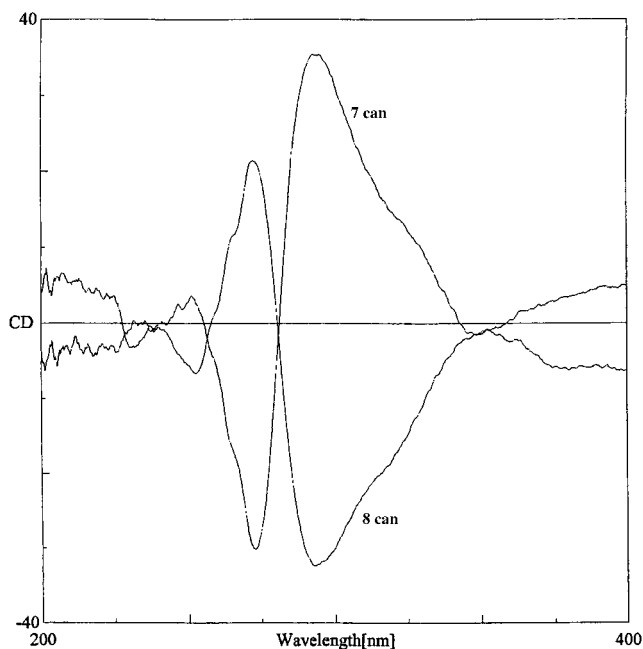


Figure 4. CD spectra of **7can** and **8can** in Nujol mull.

suspension of powdered **7** prepared by mixing gave the corresponding photocyclization products **3**. Conversion, chemical, and optical yields of these reactions are summarized in Table 3. Interestingly, **7ba** prepared from ether was unreactive, but **7ba** prepared by mixing was reactive. The IR spectrum of **7ba** prepared by mixing was different to that of **7ba** prepared from ether by IR spectroscopy due to different polymorphs being produced.

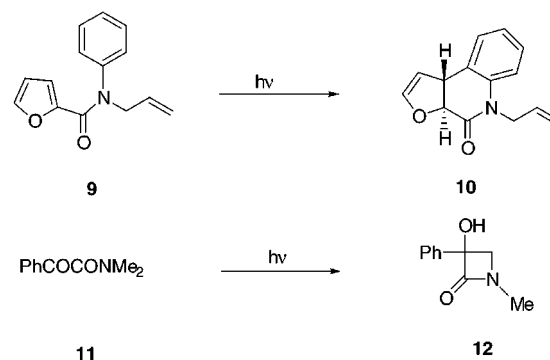
Several very efficient enantioselective photoreactions of achiral guest compounds in inclusion complexes with chiral host compounds have been reported so far.⁶⁻⁸ In some of these cases, complexation of chiral host and achiral guest gives dimorphic inclusion crystals which upon photolysis give different photoreaction products. For example, inclusion complexation of *N*-allylfuran-2-carboxyanilide (**9**) with the host **5b** gave two inclusion

Table 3. Photoreaction of **7** Prepared by Mixing of **5** and **1**

inclusion compound	irradiation time (h)	product	product		
			conv (%)	yield (%)	optical purity (% ee)
7aa	20	(+)- 3a ^a	68	4	85
7ba	15	(+)- 3a ^b	53	2	30
7cap	15	(+)- 3a ^c	47	5	88
7ab	28	(-)- 3b	89	41	94
7bb	75	(-)- 3b	61	42	85
7cb	115	(-)- 3b	46	22	62
7ac	36	(-)- 3c	64	23	59
7bc	24	(-)- 3c	82	36	83
7cc	48	(-)- 3c	80	12	50

^a **4** was obtained in 23% yield. ^b **4** was obtained 4% yield. ^c **4** was obtained in 2% yield.

compounds of 1:1 and 2:1 host:guest ratios which upon irradiation gave the (-)- (50% yield, 96% ee) and (+)- (86% yield, 98% ee) *trans*-photocyclization products **10** in the chemical and optical yields indicated.^{6a} In the inclusion complexation of *N,N*-dimethylphenylglyoxylamide (**11**) with the host **5c**, dimorphic crystals were formed depending on different of complexation methods. Recrystallization of **5c** and **11** from toluene gave their 2:1 inclusion complex which upon photolysis gave (-)-2-hydroxyl-1-methyl-2-phenylazetididin-2-one (**12**) of 85% ee in 39% yield. However, mixing of **5c** and **11** in the



absence of solvent gave their 2:1 inclusion complex which upon photolysis gave (+)-**12** of 41% ee in 48% yield.^{8d} It is very interesting that chiral arrangement of the achiral **11** molecule in the inclusion crystal is opposite depending on the method of the complexation. Nevertheless, formation of dimorphic crystals of photochemically active (**7cap**) and inactive inclusion complexes (**7can**) from **5** and **1** is the first such example.

Experimental Section

Preparation of inclusion compounds of **3** with the host **5a** and **5c**, and with **5b**, was carried out by recrystallization from toluene and ether, respectively. All inclusion compounds were formed with a 1:1 host:guest ratio. The ratio was determined by elemental analysis and measurement of ¹H NMR spectra. Photolysis of the inclusion compounds in a water suspension at room temperature was carried out through a Pyrex filter by using a 100- or 400-W high-pressure Hg-lamp. IR spectra were measured with an IR spectrometer, JASCO FT/IR-350.

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¹H NMR spectra were recorded in CDCl₃ on a JEOL JNM-LA300 (300 MHz) spectrometer. All [α]_D values were measured with a digital polarimeter, JASCO DIP-1000S. Optical purities were determined by HPLC using hexane/2-propanol (9:1) solvent unless otherwise stated (flow rate: 0.35 mL/min) and a column (0.46 cm × 25 cm) containing the chiral solid phase, Chiralcel OJ, which is commercially available from Daicel Chemical Industries Ltd., Himeji, Japan.

Preparation of 1a, 1b, and 1c. **1a–c** were prepared by a literature procedure.¹ **3-(*N*-methylanilino)-5,5-dimethylcyclohex-2-en-1-one (1a)** (colorless prisms, mp 80 °C, IR (Nujol) ν_{max} 1620 cm⁻¹, ¹H NMR δ 7.10–7.44 (m, 5 H), 5.33 (s, 1 H), 3.24 (s, 1 H), 2.18 (s, 2 H), 2.06 (s, 2 H), 1.00 (s, 6 H)); **3-(*N*-methylanilino)-2-methylcyclohex-2-en-1-one (1b)** (colorless oil, IR (Nujol) ν_{max} 1655 cm⁻¹, ¹H NMR δ 6.80–7.31 (m, 5 H), 3.24 (s, 3 H), 2.42–2.65 (m, 4 H), 1.92–2.00 (m, 2 H), 1.60 (s, 3 H)); **3-(*N*-methylanilino)-2,5,5-trimethylcyclohex-2-en-1-one (1c)** (colorless oil, IR (Nujol) ν_{max} 1655 cm⁻¹, ¹H NMR δ 6.79–7.31 (m, 5 H), 3.21 (s, 3 H), 2.32–2.36 (d, 4 H), 1.63 (s, 3 H), 1.08 (s, 6 H)).

Preparation of 1:1 Inclusion Compounds 7 by Recrystallization Method. When a solution of **5a** (2.03 g, 4.36 mmol) and **1a** (1.00 g, 4.36 mmol) in toluene (20 mL) was kept at room temperature for 12 h, a 1:1 inclusion compound of **7aa** was obtained as colorless prisms (2.42 g, 80% yield, mp 114–116 °C): IR (Nujol) ν_{max} 3167 and 1600 cm⁻¹. Anal. Calcd for C₄₆H₄₉NO₅: C, 79.39; H, 7.10; N, 2.01. Found: C, 79.25; H, 7.33; N, 2.02. By the same procedure, the following inclusion compounds were prepared. **7ba** (colorless needles, 85% yield, mp 136–138 °C): IR (Nujol) ν_{max} 3270 and 1590 cm⁻¹. Anal. Calcd for C₄₈H₅₁NO₅: C, 79.86; H, 7.12; N, 1.94. Found: C, 79.91; H, 7.35; N, 1.90. **7cap** (colorless prisms, 97% yield, mp 146–148 °C): IR (Nujol) ν_{max} 3296 and 1582 cm⁻¹. Anal. Calcd for C₄₉H₅₃NO₅: C, 79.97; H, 7.26; N, 1.90. Found: C, 80.01; H, 7.24; N, 1.88. **7can** (colorless needles, 82% yield, mp 148–150 °C): IR (Nujol) ν_{max} 3292 and 1590 cm⁻¹. Anal. Calcd for C₄₉H₅₃NO₅: C, 79.97; H, 7.20; N, 1.90. Found: C, 80.06; H, 7.48; N, 1.92. **7ab** (colorless needles, 90% yield, mp 133–135 °C): IR (Nujol) ν_{max} 3255 and 1625 cm⁻¹. Anal. Calcd for C₄₆H₄₉NO₅: C, 79.39; H, 7.10; N, 2.01. Found: C, 79.46; H, 6.99; N, 1.95. **7bb** (colorless needles, 84% yield, mp 141–145 °C): IR (Nujol) ν_{max} 3247 and 1618 cm⁻¹. Anal. Calcd for C₄₈H₅₁NO₅: C, 79.86; H, 7.12; N, 1.94. Found: C, 80.05; H, 7.06; N, 1.88. **7cb** (colorless prisms, 86% yield, mp 122–129

°C): IR (Nujol) ν_{max} 3246 and 1619 cm⁻¹. Anal. Calcd for C₄₉H₅₃NO₅: C, 79.97; H, 7.26; N, 1.90. Found: C, 79.90; H, 7.21; N, 1.68.

Photocyclization of 1 to 3. A suspension of powdered **7aa** (3.07 g, 4.41 mmol) in water (120 mL) containing hexadecyltrimethylammonium bromide (0.1 g) as a surfactant was irradiated under stirring for 16 h with 100-W high-pressure Hg-lamp. The reaction mixture was filtered, dried, and chromatographed on silica gel using AcOEt–toluene (1:9) as an eluent to give (+)-**3a** of 97% ee after distillation at 180 °C/2 mmHg as colorless oil (0.0176 g, 29% conversion, 6% yield, [α]_D +202° (c 0.1, MeOH)): IR (Nujol) ν_{max} 1705 cm⁻¹, ¹H NMR δ 7.15 (t, 1 H), 7.03 (d, 1 H), 6.68 (t, 1 H), 6.47 (d, 1 H), 4.05 (m, 1 H), 3.86 (d, 1 H), 2.76 (s, 3 H), 2.20 (q, 2 H), 1.76 (m, 1 H), 1.55 (m, 1 H), 1.00 (d, 6 H). **4¹** was obtained in 16% yield together with (+)-**3a**. By the same procedure, irradiation with 400-W high-pressure Hg-lamp of **7ab** gave (–)-**3b** of 94% ee as colorless prisms (86% conversion, 43% yield, mp 68–74 °C, [α]_D –250° (c 0.1, MeOH)): IR (Nujol) ν_{max} 1710 cm⁻¹, ¹H NMR δ 7.57 (d, 1 H), 7.16 (t, 1 H), 6.86 (t, 1 H), 6.66 (d, 1 H), 2.48–2.84 (m, 5 H), 2.29–2.47 (m, 1 H), 1.74–2.46 (m, 4 H), 1.34 (d, 3 H). Anal. Calcd for C₁₄H₁₇NO: C, 78.10; H, 7.96; N, 6.51. Found: C, 77.92; H, 8.11; N, 6.26.

Preparation of 7 by Mixing Method. For example, **7ac** was prepared by mixing powdered **5a** and **1c** for 1 h at room temperature (25 °C) using a planetary micromill, Fritsch pulverizette 7.

Photocyclization of 1c to 3c. A suspension of powdered **7ac** (1.42 g, 2.00 mmol) in water (120 mL) containing hexadecyltrimethylammonium bromide (0.1 g) as a surfactant was irradiated under stirring for 36 h with 100-W high-pressure Hg-lamp. The reaction mixture was filtered, dried, and chromatographed on silica gel using AcOEt–toluene (1:9) as an eluent to give (–)-**3c** of 59% ee as colorless prisms (0.071 g, 64% conversion, 23% yield, [α]_D –171° (c 0.1, MeOH)): IR (Nujol) ν_{max} 1705 cm⁻¹, ¹H NMR δ 7.53 (d, 1 H), 7.16 (t, 1 H), 6.86 (t, 1 H), 6.66 (d, 1 H), 2.82–2.88 (q, 1 H), 2.68 (s, 3 H), 1.96–2.14 (m, 2 H), 1.78–1.84 (m, 1 H), 1.23 (s, 3 H), 1.28 (s, 3 H), 1.06 (s, 3 H). Anal. Calcd for C₁₆H₂₁NO: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.80; H, 8.62; N, 5.88.

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