Synthesis of new Thebaine Derivatives with Phenylsulfonylpropadiene

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Reactions of thebaine with phenylsulfonylpropadiene in various solvents were investigated. It was found that Diels-Alder reaction adduct was obtained in nonpolar solvent, while addition reaction adduct was obtained in polar solvent. Transformations of these two products were also carried out.

Introduction

Thebaine 1, a unique morphine alkaloid[1,2], is too toxic to be used as an analgesic. Owing to its diene structure, however, Diels-Alder reactions of thebaine 1 with various dienophiles[3] and chemical transformations for the resulting adduct obtained have been extensively investigated.[3-6] Many of compounds derived from these reactions have shown high analgesic activity.[3a] During the course of our studies on chemical modifications of thebaine 1, we found that thebaine 1 also underwent Diels-Alder reaction or novel addition reaction with phenylsulfonylpropadiene 2[5c,7,8], depending on the solvents

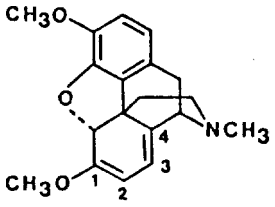
Result and Discussion

In order to predict the reactivity of dienophile 2, we calculated the CNDO/2 of compounds 1, 2 and allene as shown in Tables 1, 2 and 3. The CNDO/2 calculation data of compound 2 indicate that the introduction of a sulfonyl group causes a remarkable lowering of the LUMO energy level as compared to allene ($E = 0.1277$ a.u.) and that the largest LUMO coefficient locates on the carbon 1 and 2, due to the favorable LUMO (2)-HOMO (1) interactions as shown on Figure 1.

It was also found that: (i) The above Diels-Alder reaction took normal electron demand ($\Delta E_1 < \Delta E_2$, where; $\Delta E_1 = E^{(2)}$ LUMO-$E^{(1)}$ HOMO. $\Delta E_2 = E^{(1)} = E^{(1)}$ LUMO-$E^{(2)}$ HOMO), and frontier molecular orbital methods predicted a major regioisomer[9] as shown in Figure 2.

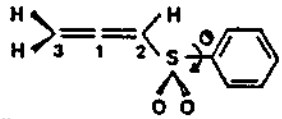
(ii) When electron withdrawing group is substituted, LUMO energies of dienophile is reduced and the reactivity is increased. (iii) When electron withdrawing group is substi-

Table 1. Frontier Molecular Orbital of Thebaine



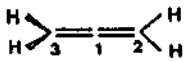
	HOMO					LUMO				
	C_1	C_2	C_3	C_4	Energy(a.u)	C_1	C_2	C_3	C_4	Energy(a.u)
A	−0.378	−0.437	0.319	0.423	−0.3995	0.351	−0.358	−0.054	0.329	0.0544
B	−0.379	−0.457	0.318	0.442	−0.3851	−0.533	0.311	0.445	−0.473	0.1263

Table 2. Frontier Molecular Orbital of Phenylsulfonylpropadiene



0	E_T(a.u.)		HOMO				LUMO			
			C_3	C_1	C_2	Energy(a.u)	C_3'	C_1	C_2	Energy(a.u)
0	−117.202995	P_x	0.211	−0.417	−0.544	−0.4883	−0.046	−0.316	0.173	0.0576
		P_r	0.342	0.169	−0.276	−0.4545	−0.306	0.203	0.269	0.0809
30	−117.2031788	P_z	0.206	−0.407	−0.529	−0.7878	−0.042	−0.285	0.157	0.0568
		P_y	0.332	0.165	−0.267	−0.4556	0.312	−0.206	−0.273	0.0808
60	−117.203357	P_s	0.198	−0.392	−0.509	−0.4872	0.027	0.187	−0.103	0.0052
		P_y	−0.334	−0.168	0.268	−0.4561	−0.318	0.207	0.275	0.0808
90	−117.203473	P_z	−0.205	0.406	0.527	−0.4871	−0.096	−0.521	0.337	0.0543
		P_y	0.341	0.171	−0.274	−0.4569	−0.319	0.207	0.275	0.0810

Table 3. Frontier Molecular Orbital of Allene



E_T = 23.9657538(a.u)

E_T = 23.838887(a.u)

	HOMO				LUMO			
	C_3	C_1	C_2	Energy (a.u)	C_3	C_1	C_2	Energy (a.u)
P_z	-0.274	0.432	0.620	-0.5078	-0.185	-0.573	0.583	0.182
P_y	0.620	0.432	-0.274	-0.5078	-0.583	0.573	0.185	0.182

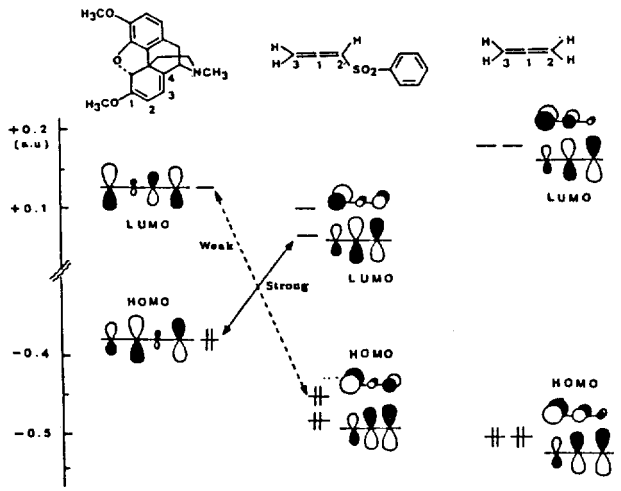


Figure 1. Frontier molecular orbital interaction of thebaine and phenylsulfonylpropadiene.

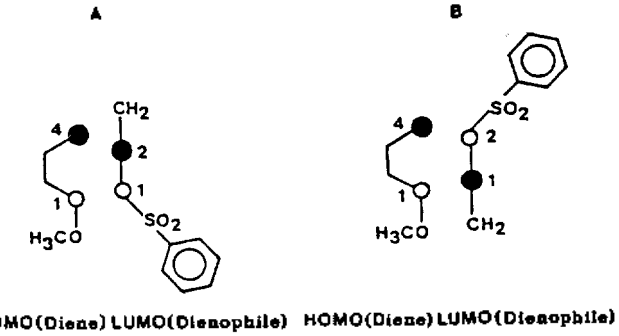
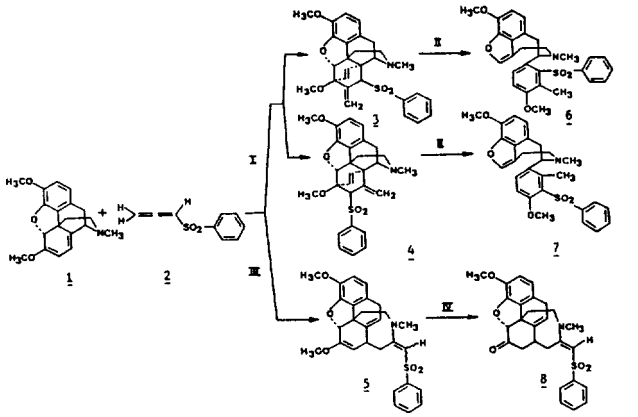


Figure 2. Concerted mechanism of thebaine and phenylsulfonylpropadiene.

tuted, the electron density of central carbon of dienophile becomes smaller and a novel nucleophilic addition will be better. Accordion to the above reactivity, Diels-Alder reaction between thebaine and a new dienophile was shown on Scheme 1.

The Diels-Alder reaction of thebaine 1 with 1.5 dq. of dienophile 2 in a sealed tube (toluene) at 120 °C provided a mixture of adducts 3 and 4 in 90% yield, which could be isolated in a pure form by column chromatography. When thebaine 1 was reacted with 1.5 eq. of dienophile 2 in methanol at room temperature, crystalline addition adduct 5 as an inseparable mixture of *E* and *Z* isomers was obtained quantitatively. However, it was found that the yield of addition adduct 5 was remarkably changed depending on the solvents. The result of reactions in various solvents were shown on Table 4.



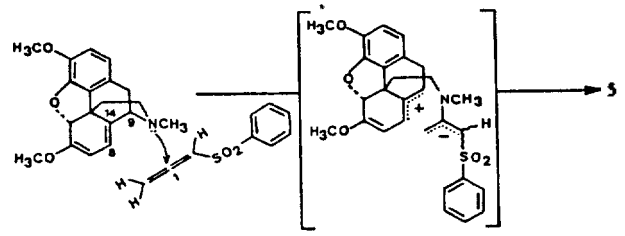
Ⅰ : Diels-Alder Reaction, Ⅱ : Thermolysis, Ⅲ : Novel Addition Reaction, Ⅳ : Hydrolysis

Scheme 1

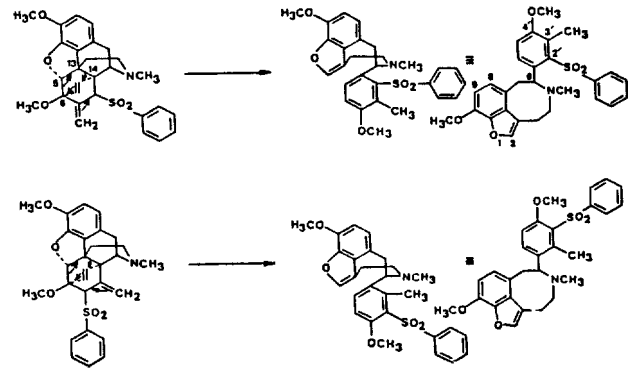
Table 4. Solvent Effect of Novel Addition Reaction at Room Temperature

Solvent[a]	Rxn. time(hr)	Yield(%)
Methanol	0.5	98
Acetonitrile	7	67
Methylene Chloride	23	43
Benzene	No rxn.	

[a] All reactions were performed at room temperature.



Scheme 2



Scheme 3

These results indicat that addition reaction between thebaine 1 and dienophile 2 occurs via zwitterionic intermidiate as shown in Scheme 2.

The reaction may be initiated by the nucleophile addition of thebaine 1 to the central carbon of dienophile 2 followed by the cleavage of C_9-N bond to give an ionic intermediate. The sterically most favorable ring closure at C_8 position of the resulting intermediate leads to the formation of adduct 5. We also investigated the thermal rearrangement of the Diels-

Alder adducts 3 and 4. When the adducts 3 and 4 were heated to reflux, the thermal isomer was thus obtained in 84% yield as a colorless glass which could not be obtained crystaline.

A suggestion as to the structure of the thermally rearranged adduct came from the various reports on the pyrolysis of some Diels-Alder adducts of DMA[10]. The thermal rearrangement of adducts 3 and 4 was formulated as proceeding through disruption of the allylic $C_{5,6}$ and $C_{13,14}$ bonds to give the adduct 6 and 7 as shown on Scheme 3. Finally, acid hydrolysis of adduct 5 with conc. HCl-THF (1:40) provided ketone 8 in 75% yield.

Experimental

The IR spectra were obtained by using a Pye Unicam sp3300 spectrophotometer and the ^{1}H nmr spectra were taken with a Bruker wp 80 cw and FT 200MHz spectrometer with TMS as an internal standard. The melting points were measured with a Schimadzu Thermal Analizer DT-30 and are uncorrected. Starting material phenylsulfonylpropadiene 2 was prepared according to the reported methods. Column chromatography was performed by using E. M. Merck keselgel 60(70-240 mesh) as stationary phase.

17-Methyl-18-phenylsulfonyl-6,14-ethenocodeine methyl ether (3) and 17-phenylsulfonyl-18-methenyl-6,14-ethenocodeine methyl ether(4). A solution of 233.3 mg (0.75 moles) of 1 and 90.2 mg (0.50 mmoles) of 2 in 3 m*l* dry toluene was allowed to react at 120 °C for 5 hours in a sealed tube. The reaction mixtures was cooled to room temperature, followed by removal of the solvent. The oily residue was chromatographed on a silica gel column with ethyl acetate/n-hexane (3:1) as an eluant to give adduct 3 (145.0 mg; 40.5%) M.P. 209-210 °C ^{1}H NMR ($CDCl_3$) δ1.60(*s*, C_7-CH_2), 2.10(*s*, N-CH_3), 3.80(*s*, C_6-OCH_3), 3.90(*s*, C_3-OCH_3), IR(KRr) Cm^{-1} 3100 (=CH_2), 1430-1490 (SO_2) and adduct 4 (118.8 mg; 49.5%) M.P. 203-202 °C, ^{1}H NMR($CDCl_3$) δ1.30 (*s*, C_8-CH_2), 2.02(*s*, N-CH_3), 3.70(*s*, C_6-OCH_3), 3.91(*s*, C_3-OCH_3).

Thebaine-Phenylsulfonylpropadiene novel adduct (5). A solution of 233.3 mg (0.75 mmoles) of 1 in 10 m*l* of dry methanol and 90.2 mg (0.50 mmoles) of 2 in 5 m*l* of dry methanol was stirred at room temperature for 30 minutes, and then evaporated to provide 311.8 mg(98%) of the novel adduct 5, as an inseparable mixture (2:1) of *E* and *Z* isomer identified on NMR. ^{1}H NMR($CDCl_3$) δ2.78(*s*, N-CH_3), 3.45(*s*, C_6-OCH_3(E)), 3.55(*s*, C_6-OCH_3(Z)), 3.84(*s*, C_3-OCH_3), 4.73 (br.*s*, C_{20}-H(Z)), 5.16(br.*s*, C_{20}-H(E)).

6-(2′-phenylsulfonyl-3′-methyl-4′-methoxyphenyl)-10-methoxy-5-methyl-3,4,6,7-thtrahydrofuro-5H-(4,3,2-fg) (3) benzazocine (6) and 6-(2′-Methyl-3′-phenylsulfonyl-4′-methoxyphenyl)-10-methoxy-5-methyl-3,4,6,7-tetrahydrofuro-5H-(4,3,2-fg) (3) benzazocine (7). To 10 m*l* of anhydrous ethylene glycol mono-n-butyl ether were added 70 mg (0.142 mmoles) of adducts 3 and 4, and the mixture was heated to reflux for a period of 15 minutes. The solvent was removed under reduced pressure and the tan residue was dissolved in benzene (20 m*l*) and extracted with 0.5M phosphoric acid (4 × 15 m*l*). After a benzene wash (2 × 10 m*l*), the combined acidic extracts were neutralized (pH7) with saturated aqueous sodium carbonate. The suspension was extracted with methylene chloride (4 × 15 m*l*) and the combined organic extracts were washed with 20 m*l* of 0.3M phosphate buffer, dried and evaporated to provide 59.0 mg(84%) of thermal isomers 6 and 7 as a colorless glass. Isomer 6: M.P. 301 °C, IR(KBr) cm^{-1} 1450(CH_3), ^{1}H NMR($CDCl_3$)δ1.80(*s*, C_3-CH_3), 1.96(*s*, N-CH_3), 3.81(C_4-OCH_3), 4.10(*s*, C_{10}-OCH_3), 6.90(*D*, $C_{5,6}$-H), 7.40(*s*, C_2- H) Isomer 7: 73% yield, M.P. 294-296 °C, ^{1}H NMR($CDCl_3$) 1.62(*s*, C_3′-CH_3), 1.94(*s*, N-CH_3), 3.90(C_4′-OCH_3), 4.10(*s*, C_{10}-OCH_3), 7.40(*s*, C_2- H).

Thebaine-Phenylsulfonylpropadiene hydrolized isomer(8). An *E-Z* mixture of 70 mg (0.147 mmoles) of 5 was treated with conc. HCl-THF(1:40) at room temperature for 2 hours, dried and evaporated to provide 52.5 mg (75%) on the ketone 8, as a sole themodynamic product. M.P. 279-280 °C IR(KBr) Cm^{-1} 1700(C=O), ^{1}H NMR($CDCl_3$)δ2.83(*s*, N-CH_3), 3.90(*s*, C_6-OCH_3), 5.09(*s*, C_{20}-H).

Acknowledgement. Financial support by the Korea Science and Engineering Foundation is gratefully acknowledged.

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^{19}F NMR Studies on 8,9-Dehydro-2-adamantyl and 2,4-Dehydro-5-homoadamantyl Cations

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To probe the geometrical effects of cyclopropyl moiety on the stabilization of an adjacent cation center, ^{19}F chemical shift of 2-p-fluorophenyl-8,9-dehydro-2-adamantyl cation (3) was compared with that of 5-p-fluorophenyl-2,4-dehydro-5-homoadamantyl cation (4). Difference between the ^{19}F chemical shift of 8,9-dehydro-2-adamantyl cation 3 and that of 2,4-dehydro-5-adamantyl cation 4 is 5.1 ppm ($\Delta\Delta\delta$). We conclude, therefore, that ion 3 is about 3.82 kcal more stable than ion 4 of which rigid carbon skeleton requires significant distortion of the cyclopropane ring from the ideal bisected conformation. The energy difference between these cations can be calculated by Taft-Relationship[8] on the basis of ^{19}F chemical shift.

Introduction

It is generally conceded that the bisected conformation of cyclopropylcarbinyl cations is the most stable[1]. Molecular orbital calculations[2] indicate that there is stabilization of 9-16 kcal/mol between the bisected (1) and perpandicular (2) conformations (Figure 1). It is in the bisected orientation that the cyclopropyl moiety exhibits the largest stabilizing effect on an adjacent positively charged center whereas it destabilizes a carbenium ion when fixed in a perpendicular orientation. In the case of secondary and tertiary cyclopropylcarbinyl cations, nmr studies have led to conclusion that these ions exist in the bisected arrangement[3]. In our previous ^{19}F nmr study[4], we have shown that the electronic effects were very sensitive to the conformation of the cyclopropane ring toward the vacant p orbital in rigid cyclopropylcarbinyl cations. We here report our results of ^{19}F nmr studies on 2-p-fluorophenyl-8,9-dehydro-2-adamantyl (3) and 5-p-fluorophenyl-2,4-dehydro-5-homoadmantyl cations (4) under stable ion condition.

8,9-Dehydro-2-adamantyl cation 3 is one of the most typical systems which geometrically constrained. Since its feature is the symmetrical bisected conformation[5], it may be most favored for the σ-conjunctive interaction between a strained cyclopropyl moiety and an adjacent cation center. In contrast, 2,4-dehydro-5-homoadamantyl cation 4 has a geometry in which rigid carbon skeleton requires slight distortion of the cyclopropane ring from the bisected conformation.

In view of these points, we were interested in the examining the relative stability of 8,9-dehydro-2-adamantyl cation 3 and 2,4-dehydro-5-homoadamantyl cation 4 using ^{19}F nmr parameters. Despite of similar nuclear properties of fluorine 19 and protone, there is an essential difference in the nmr parameters of the two nuclears. Whereas proton chemical shifts are usually confined to a range of 13 ppm, the resonance of fluorine encompasses a much broad range of approximately 500 ppm[6]. Therefore, ^{19}F-nmr has a advantage of the great sensitivity compared to ^{1}H-nmr, and the comparative insensitivity to magenetic anisotropies of solvent and molecule.

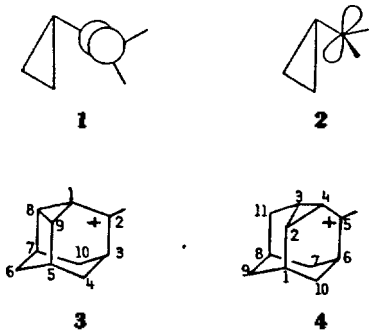

Figure 1.

It has been known that the fluorine nuclear magnetic resonance shielding or p-fluorophenyl derivatives is predominantly determined by the MO theory π-electron charge density at the p-carbon atom since the former is apparently directly related to the latter[7].

Thus there is theoretical basis for both direct shielding-π-charge density and shielding-π-electronic energy relationship. The latter relationship, however, can be directly utilized in the understanding of correlation between substituent shielding and reactivity parameter. A linear correlation of fluorine nmr parameters with the stabilization energy for substituted tritylcations was observed by Taft[8].

Using the Taft's ^{19}F chemical shifts correlation(line of slope; 1 ppm/0.75 kcal), therefore, we were compared to the relative stability and calculated a difference of stabilization energy between ion 3 and 4, and these results are described in this paper.

Experimental

^{1}H nmr spectra were obtained in $CDCl_3$ at 100 MHz, using a Varian XL-100 instrument, and chemical shifts were referenced from internal TMS. Cation solutions were made up