Tetrahedron Vol. 46, No. 12, pp 4371–4378, 1990
Printed in Great Britain

0040-4020/90 $3.00+.00

5-METHYLENE-2(5H)-FURANONE IN DIELS-ALDER REACTIONS WITH CYCLIC DIENES: endo/exo SELECTIVITY.

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(*Received in UK 9 April* 1990)

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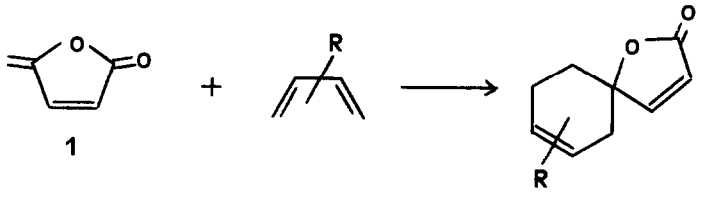
Abstract.- Endo/exo selectivity in the reactions of 5-methylene-2(5H)-furanone, **1**, with cyclic dienes has been investigated. Both the kinetic and theoretical studies of the cycloaddition between **1** and cyclopentadiene have permitted to explain the observed selectivity as a direct consequence of a kinetic control over the process.

INTRODUCTION

In a previous paper[1] we have reported that 5-methylene-2(5H)-furanone (protoanemonin), **1**,[2] reacts specifically at the exocyclic double bond (site-selectivity) with a wide variety of acyclic dienes to produce bicyclic spiro adducts in good yields (Scheme 1). This selectivity has been interpreted by means of theoretical calculations, invoking both electronic and steric factors. Regioselectivity in the cycloaddition to unsymmetrically substituted dienes has also been investigated. Thus, reaction with isoprene afforded a mixture of the two possible regioisomers in a temperature dependent ratio. However, reactions with 1-substituted dienes, such as piperylene and 1,3-dimethylbutadiene, yielded a single regioisomer in each case.



Scheme 1

In the present paper we describe the cycloadditions of protoanemonin **1** with two representative cyclic dienes, cyclopentadiene and cyclohexadiene, focussing our attention on the endo/exo stereoselectivity. The new tricyclic

adducts obtained in these reactions are virtual precursors of diversely functionalized derivatives of norbornane and of bicyclo [2.2.2] octane, respectively, showing thus their importance as synthetic building blocks.

RESULTS AND DISCUSSION

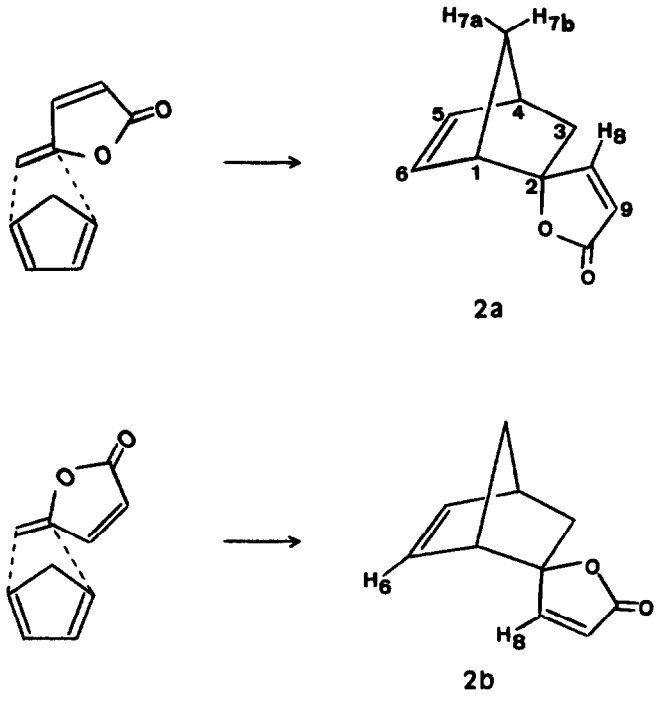
Lactone 1 was made to react with cyclopentadiene, using dichloromethane as solvent, at the temperatures shown in Table 1. A mixture

Table 1. Reactions of protoanemonin, 1, with cyclopentadiene and cyclohexadiene, giving adducts 2 and 3, respectively.

Diene	Temperature (°C)	Time (h)	a/b[a]
Cyclopentadiene(b)	60	70.7	2.60
Id.	85	62.3	2.55
Id.	100	62.0	2.46
Id.	135	7.0	2.26
Id.	160	7.5	2.22
Cyclohexadiene[c]	60	70.2	1.49
Id.	85	62.0	1.48
Id.	100	61.5	1.47
Id.	135	6.7	1.46
Id.	160	6.5	0.19

[a] Determined by G.C. [b] 70-80% Yield. [c] 60-70% Yield.

of the tricyclic stereoisomers **2a,b** was obtained in 70-80% yield, being **2a** the major product (Scheme 2). (The structural assignment is discussed below). The **2a/2b** ratio was temperature dependent, the proportion of **2b** increasing moderately at high reaction temperatures. Products arising from the attack of the diene at the endocyclic double bond of protoanemonin, 1, were never detected.



Scheme 2

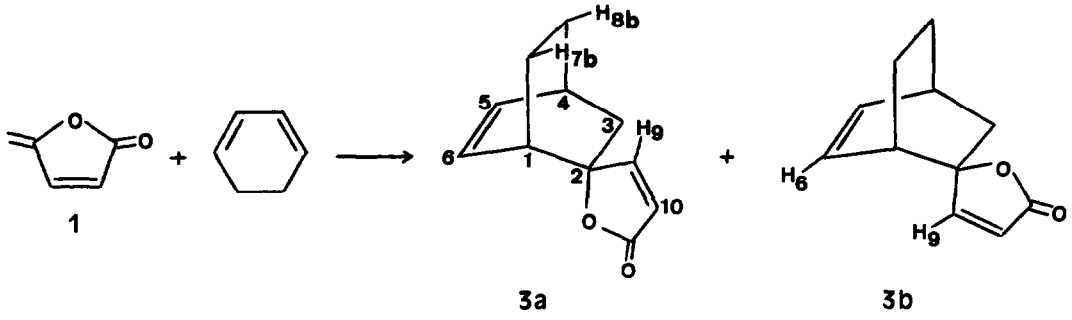
In a similar way, reactions of **1** with cyclohexadiene were performed at temperatures shown in Table 1, giving the tricyclic adducts **3a,b** in 60-70% yields (Scheme 3). In the 60-135 °C range of temperatures compound **3a**, homologous of **2a**, was the major product. The ratio was reversed at high temperature, but this result is misleading, since 1:2 protoanemonin-cyclohexadiene adducts were detected as minor products (NMR, MS) at 160 °C, this fact masking the true yield in each stereoisomer.

The four compounds **2a**, **2b**, **3a**, and **3b**, were isolated by column chromatography and completely characterized. Their structures were elucidated mainly by 400 MHz ^{1}H NMR spectral analysis. Simple chemical shift arguments suggest that in 2-series the proton endo-H_8 should appear upfield because of interaction with the double bond. The same applies to endo-H_9 in 3-series. These structures were also confirmed from differential NOE experiments which allowed to assign unequivocally the stereochemistry of each product.[3] Results are given in Table 2 and show a significant spacial proximity between H_8 and one of the bridge protons (i.e., H_{7b}) in **2a**, and

Table 2. Chemical shifts (ppm), couplings, J(s) (Hz) and NOEs (%) for the protons in adducts **2a**, **2b**, **3a**, and **3b**.

Adduct	Proton[a]		Signal	J	J'	J''	NOE
2a	1	2.86	m	-	-	-	0.95
	3n	1.51	m	-	-	-	-
	3x	2.07	dd	12.78	3.64	-	1.4
	4	3.05	m	-	-	-	-
	5	6.46	ddd	5.65	3.09	0.65	0.2
	6	6.20	dd	5.65	2.99	-	0.15
	7a+7b	1.62	m	-	-	-	3.5
	8	7.51	d	5.55	-	-	irradiated
	9	6.03	d	5.55	-	-	5.4
2b	1	2.77	m	-	-	-	0.7
	3n	1.62	dd	12.65	2.88	-	1.7
	3x	2.04	dd	12.65	3.56	-	-
	4	3.06	m	-	-	-	-
	5	6.44	dd	5.73	3.00	-	0.3
	6	6.06	dd	5.73	3.07	-	1.85
	7a	1.78	m	-	-	-	-
	7b	2.06	m	-	-	-	-
	8	7.15	d	5.58	-	-	irradiated
	9	6.01	d	5.58	-	-	5.8
3a	1	2.52	m	-	-	-	0.5
	3x	1.84	dd	14.08	2.34	-	1.5
	3n+7b	1.70	m	-	-	-	3.4
	4	2.76	m	-	-	-	0.1
	5	6.45	ddd	8.27	6.59	1.08	-
	6	6.32	ddd	8.27	6.25	0.90	-
	7a+8a+8b	1.41	m	-	-	-	-
	9	7.54	d	5.64	-	-	irradiated
	10	6.02	d	5.64	-	-	3.6
3b	1	2.44	m	-	-	-	0.9
	3n+3x+8b	1.73	m	-	-	-	2.3
	4	2.74	m	-	-	-	-
	5	6.44	ddd	8.27	6.44	1.05	0.5
	6	6.23	ddd	8.27	6.68	1.28	1.5
	7a+7b	1.32	m	-	-	-	-
	8a	2.22	m	-	-	-	0.15
	9	7.18	d	5.52	-	-	irradiated
	10	5.92	d	5.52	-	-	5.8

[a] n Stands for endo, x stands for exo.



Scheme 3

between the couple of protons H_8 and H_6 in **2b**. Thus, the major product was identified as the isomer endo **2a**, in which the lactone ring oxygen occupies the endo position of the norbornene system, and **2b** as the exo isomer.

Similarly, adducts derived from **1** and cyclohexadiene were also elucidated, the major product being again the endo stereoisomer **3a**.

A kinetic study of the reaction between **1** and cyclopentadiene was carried out at 60, 135, and 160 °C, using an excess of diene (4 equivalents). First, it was confirmed that stereoisomer ratio remained constant throghout the course of each reaction. This result indicates that there is not endo-exo isomerization during the process and that none stereoisomer is consumed by preferential reaction with excess cyclopentadiene.

Measurements of the relative yields of the product isomers were made at the temperatures shown on Table 1 (See Experimental Part). Assuming a kinetic control of the reaction, the endo/exo product ratio (a/b) was considered to be equal to the ratio of the rate constants k_a/k_b. The difference between the activation energies of the two processes was evaluated by plotting ln(a/b) against 1/T. In this way, an energy gap of about 0.5 kcal/mol was found.

This value is in good agreement with that determined by theoretical calculations, using the MNDO method. The theoretical study of this reaction led to predict that the formation of compound **2a** is the kinetically more favourable, the difference of energy barriers being 0.6 kcal/mol. The calculations also showed that the formation of both adducts proceeds via a very asynchronous mechanism. The structures of the transition states are presented in Figure 1. One can observe that in both cases one new C-C bond

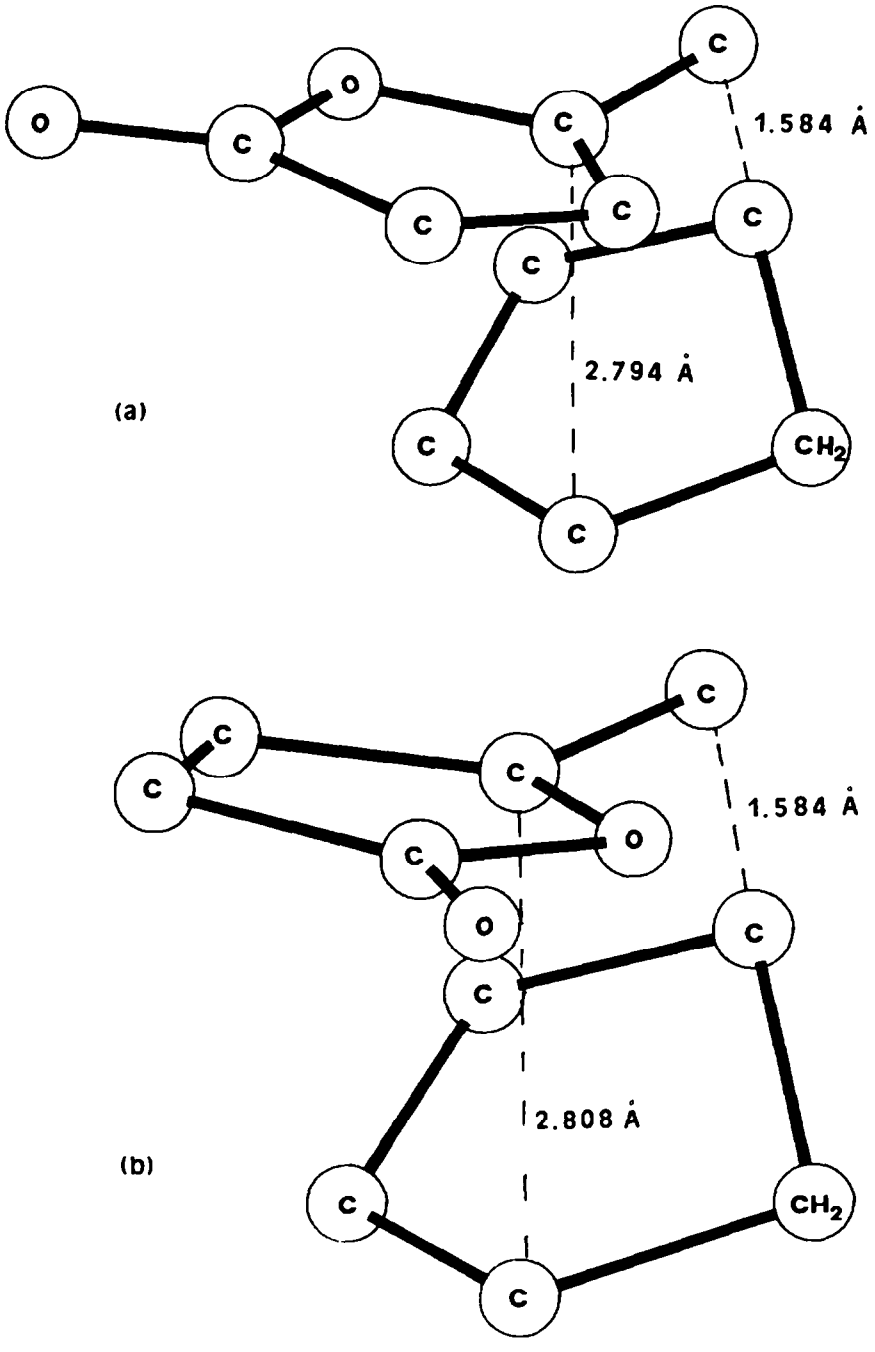


Fig. 1. Structures of the endo (a) and exo (b) transition states.

is almost completely formed while the other still presents a very long C-C distance. According to these results, the reaction seems to occur through a one step - two stage process.

In the case of reactions with cyclohexadiene, the calculated difference of energy barriers was only 0.2 kcal/mol, in accordance with the experimentally observed lower selectivity.

As conclusion, we have shown that protcanemonin, **1**, reacts at the exocyclic double bond with cyclic dienes giving adducts in good yields with moderate endo/exo selectivity. This stereoselectivity is lower than that observed in the cycloadditions of chiral 5-substituted 2(5H)-furanones, these compounds reacting by the sole endocyclic double bond.[4] Kinetic measurements and theoretical calculations have permitted to interpret the selectivity in the reactions of **1** as a consequence of kinetic control over the process.

EXPERIMENTAL SECTION

Melting points were determined in a hot stage and are uncorrected. The electron-impact mass spectra were recorded at 70 eV.

General Procedure for Theoretical Calculations. The MNDO method[5] has been used in the energy calculation. Transition states have been localized by means of the McIver and Komornicki's method[6] and characterized by checking the eigenvalues of the force constant matrix. All calculations have been carried out with the AMPAC program.[7]

General Experimental Procedures. Reactions of protoanemonin, **1** with cyclopentadiene and cyclohexadiene were performed at 60, 85, 100, 135, and 160 °C, respectively. Reaction time in each case is shown in Table 1. These reactions were conducted in sealed tubes containing 4 mmol of **1** and 16 mmol of diene in 16 mL of dichloromethane (0.6 M in **1**).

The kinetic study of the cycloaddition between **1** and cyclopentadiene was effected at 60, 135, 160 + 0.5 °C. At intervals, three tubes were cooled, opened, concentrated, and analysed by gas chromatography. The proportion of endo/exo (a/b) isomers was determined from the ratio of peak areas using naphtalene as internal standard. The response factor of each adduct and the starting lactone **1** were obtained *vs* the internal standard through calibration curves. The operation was carried out at five time intervals.

All adducts were purified by column chromatography on silica gel, using mixtures of hexane-ethyl acetate as eluents. Their physical and further spectroscopic data are the following:

(1SR,2SR,4SR)-3-(2-Hydroxybicyclo [2.2.1] hept-5-en-2-yl)prop-2-enoic acid lactone, 2a.

Crystals, m.p. 114-115° C (from hexane-ethyl acetate); ir (KBr) 1735, 1596 cm^{-1}; cmr ($CDCl_3$) 37.9, 43.1, 47.6, 51.2, 94.9, 119.4, 133.1, 139.0, 160.5, 172.5; ms, m/e (relative intensity) 162 (M^+, 3.5), 133 (0.8), 115 (0.9), 105 (0.6), 97 (20.1), 91 (2.5), 82 (6.8), 79 (8.9), 77 (7.6), 66 (100), 54 (10.1). Anal. Calcd. for $C_{10}H_{10}O_2$: C, 74.06; H, 6.21. Found: C, 73.93; H, 6.27.

(1SR,2RS,4SR)-3-(2-Hydroxybicyclo [2.2.1] hept-5-en-2-yl)prop-2-enoic acid lactone, 2b.

Crystals, m.p. 95-97° C (from hexane-ethyl acetate); ir (KBr) 1736, 1592 cm^{-1}; cmr ($CDCl_3$) 37.5, 41.8, 48.6, 53.4, 95.4, 120.1, 131.9, 141.8, 160.0, 172.3; ms, m/e (relative intensity) 163 (M^+ + 1, 1.2), 162 (M^+, 2.4), 133 (0.7), 115 (1.0), 105 (0.7), 97 (19.5), 91 (2.2), 82 (5.4), 79 (5.7), 77 (5.8), 66 (100), 54 (9.8). Anal. Calcd. for $C_{10}H_{10}O_2$: C, 74.06; H, 6.21. Found: C, 74.18; H, 6.41.

(1SR,2SR,4SR)-3-(2-Hydroxybicyclo [2.2.2] oct-5-en-2-yl)prop-2-enoic acid lactone, 3a.

Crystals, m.p. 92-94° C (from pentane-ether); ir (KBr) 1737 and 1599 cm^{-1}; cmr ($CDCl_3$) 20.5, 22.7, 29.1, 37.6, 38.9, 91.1, 119.3, 131.2, 133.9, 159.6, 171.7; ms, m/e (relative intensity) 177 (M^+ + 1, 19.9), 97 (11.1), 80 (100.0), 79 (62.4), 77 (23.4), 54 (22.7), 51 (15.4). Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.84; H, 6.86.

(1SR,2RS,4SR)-3-(2-Hydroxybicyclo [2.2.2] oct-5-en-2-yl)prop-2-enoic acid lactone, 3b.

Crystals, m.p. 51-52° C (from pentane-eter); ir (KBr) 1762 and 1592 cm^{-1}; cmr ($CDCl_3$) 19.8, 23.2, 29.2, 34.6, 39.0, 90.4, 117.8, 130.0, 135.9, 161.0, 171.8; ms, m/e (relative intensity) 176 (M^+, 1.4), 98 (12.4), 97 (13.5), 91 (12.0), 82 (12.7), 80 (100.0), 79 (88.5), 77 (33.8), 54 (25.3), 51 (15.3). Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.78; H, 6.88.

Acknowledgements.- Financial support from "Comisión Asesora de Investigación Científica y Técnica" (project PB85-0244), and LUCTA S.A. is gratefully acknowledged.

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