Role of the $A^{1,3}$ Allylic Interaction on the Stereochemistry of Formation of Schiff's Bases derived from Bicyclo[2.2.1]hept-5-en-2-one and 7-Oxabicyclo[2.2.1]hept-5-en-2-one

Odón Arjona, Araceli Mallo, Cristina Manzano, and Joaquín Plumet*
Universidad Complutense, Facultad de Química, Departamento de Química Orgánica, 28040 Madrid, Spain
Juan Galbis*
Universidad de Sevilla, Facultad de Farmacia, Departamento de Química Orgánica, 41012 Sevilla, Spain
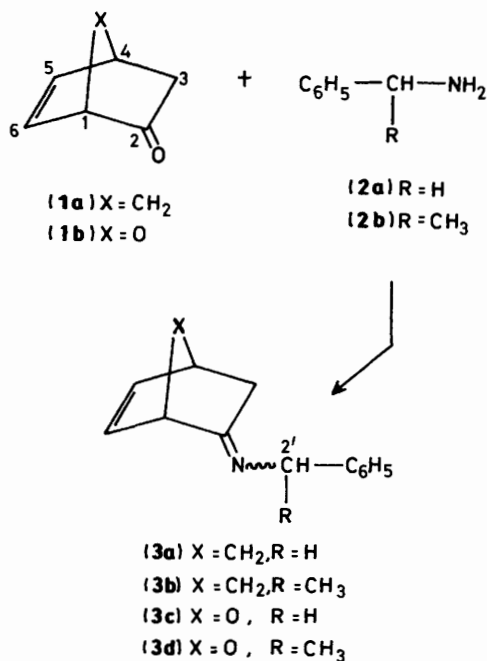**Carlos Jaime***
Universidad Autónoma de Barcelona, Facultad de Ciencias, Departamento de Química, Unidad de Química Orgánica, 08193 Bellaterra, Barcelona, Spain

The stereochemistry of formation of Schiff's bases derived from norbornen-2-one and 7-oxanorbornen-2-one has been studied by ^{1}H and ^{13}C n.m.r. spectroscopy. Elucidation of the reason for the preference for the *E*-isomer in both cases has been attempted by molecular mechanics calculations. This preference may be justified by $A^{1,3}$ allylic interactions.

The stereochemistry of formation of Schiff's bases derived from bridgehead systems has received little attention compared with analogous open-chain compounds[1] despite their potential synthetic utility.[2] Berubé and Jankowski[3] and Marshall and Hershline[4] have independently considered the stereochemistry of formation of Schiff's bases derived from norbornanone and 1-phenylethylamine, with different results. To the best of our knowledge, the stereochemistry of formation of Schiff's bases derived from norbornen-2-one and 7-oxanorbornen-2-one has not been examined yet. The objective of this report is to address this question as well as to present a theoretical explanation for the observed stereochemical preference.

Results and Discussion
Condensation of (**1a,b**) (Scheme 1) with amines (**2a,b**) in boiling benzene yielded Schiff's bases (**3a—d**) almost quantitatively.

(**1a**) X = CH$_2$
(**1b**) X = O

(**2a**) R = H
(**2b**) R = CH$_3$

(**3a**) X = CH$_2$, R = H
(**3b**) X = CH$_2$, R = CH$_3$
(**3c**) X = O, R = H
(**3d**) X = O, R = CH$_3$

Scheme 1.

For compounds (**3a** and **c**), two diastereoisomeric racemates are possible [*E*-(*R*,4*R*-1*S*,4*S*) and *Z*-(1*R*,4*R*-1*S*,4*S*)], whereas four diastereoisomeric possibilities are conceivable for compounds (**3b** and **d**) namely [*E*-(1*S*,4*S*,2*S*-1*R*,4*R*,2*R*), *Z*-(1*S*,4*S*,2*R*-1*R*,4*R*,2*S*), *E*-(1*S*,4*S*,2*R*-1*R*,4*R*,2*S*), and *Z*-(1*S*,4*S*,2*S*-1*R*,4*R*,2*R*)]. All possibilities are indicated in Scheme 2, where

E-1*S*,4*S*,2'*S*   *Z*-1*S*,4*S*,2'*R*

E-1*S*,4*S*,2'*R*   *Z*-1*S*,4*S*,2'*S*
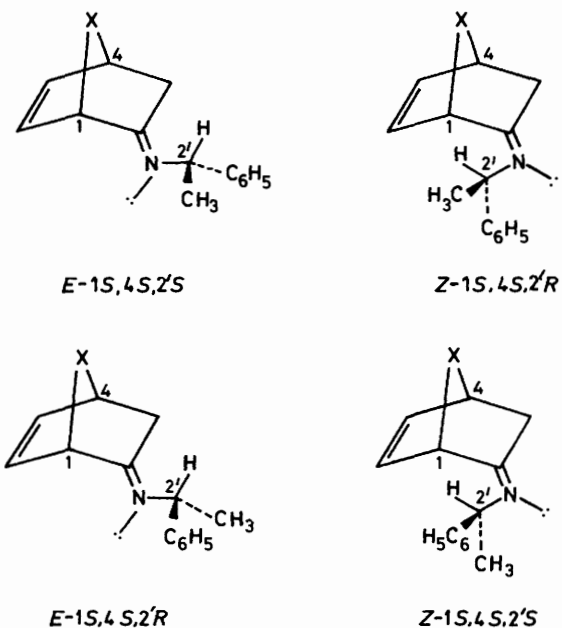
Scheme 2.

only one enantiomer for each racemate has been represented for simplicity.

The ^{1}H and ^{13}C n.m.r. spectra of imines (**3a,b**) contain signals attributable to all possible diastereoisomers (Table 1).

Thus, the ^{1}H n.m.r. spectrum of (**3a**) (CDCl$_3$; 200 MHz) has two wide singlets which could be attributed to the benzylic 2H, the more intense at δ 4.40, and the other at δ 4.60. The intensity ratio of the signals is *ca.* 10:1. The ^{13}C n.m.r. spectrum of (**3a**) also has two duplicate peaks which could be assigned to C-3 and C-2'. The peaks assigned to C-3 appear at δ 31.45 (major) and 35.83 p.p.m. (minor), while those for C-2' are at δ 57.86 (major) and 57.32 p.p.m. (minor). This difference in chemical shifts, due

Table 1. Significant n.m.r. data for E and Z isomers and $E:Z$ ratio of compounds (3a—d)

	¹H N.m.r.			¹³C N.m.r.			
Compound	Chemical shift δ (p.p.m.)	Assignment	Isomer	Chemical shift δ (p.p.m.)	Assignment	Isomer	$E:Z$ ratio
(3a)	4.40	H-2′	E	31.45	C-3	E	10:1
	4.60	H-2′	Z	35.83	C-3	Z	
				57.86	C-2′	E	
				53.72	C-2′	Z	
(3b)	4.30, 4.33	H-2′	E	23.70, 23.40	CH₃	E	8:1
	4.65, 4.68	H-2′	Z	24.49, 24.75	CH₃	Z	
	1.39, 1.48	CH₃	E	61.62, 62.10	C-2′	E	
	1.36, 1.52	CH₃	Z	61.32	C-2′	Z	
				30.48, 30.48	C-3	E	
				35.36, 35.48	C-3	Z	
(3c)	4.43	H-2′	E	82.12	C-1	E	15:1
				76.30	C-1	Z	
				29.78	C-3	E	
				33.33	C-3	Z	
				58.93	C-2′	E	
				57.93	C-2′	Z	
(3d)	4.27, 4.29	H-2′	E	27.73, 24.14	CH₃	E	10:1
	4.63	H-2′	Z	24.94, 25.36	CH₃	Z	
	1.41, 1.49	CH₃	E	63.44, 63.58	C-2′	E	
	1.39, 1.55	CH₃	Z	62.47, 62.59	C-2′	Z	
				29.09, 29.19	C-3	E	
				33.00, 33.20	C-3	Z	

to the different steric compression in both isomers, allows for the assignment of the major peak for C-3, more shielded, to the E-isomer, and of the minor to the Z-isomer. This is in good agreement with observations for C-2′, more sterically compressed in the Z-isomer (less intense signal at δ 57.32 p.p.m.).

The ¹H n.m.r. spectrum of (3b) (CDCl₃; 200 MHz) has four quartets, distributed in two pairs, which could be assigned to H-2′. One pair of quartets of higher intensity and in 1:1 ratio, are at δ 4.30 and 4.33, respectively, while the second pair, of lower intensity and also in 1:1 ratio, are at δ 4.65 and 4.68, respectively. The methyl area is significant too: an apparent triplet at δ 1.44 and two less intense doublets, at δ 1.36 and 1.52 (J 6.6 Hz) in 1:1 ratio, are observed. The intensity ratio between the apparent triplet and the two doublets is ca. 8:1.

Examination of the ¹³C n.m.r. spectrum of these compounds allows the following observations to be made: the methyl group of the 1-phenylethyl moiety appears split into four peaks, two of higher intensity (δ 23.70 and 23.97 p.p.m.) and two of lower intensity (δ 24.49 and 24.75 p.p.m.). In a similar fashion, the signals due to the methine of the same residue are tripled, as two signals of higher intensity (δ 61.72 and 62.10 p.p.m.) and another one of much lower intensity (δ 61.32 p.p.m.). Considering that this carbon atom will be more sterically compressed in the Z-isomer, the less intense signal at higher fields can be attributed to the Z-isomer. Finally, signals attributable to C-3 are quadrupled; two major signals of approximately the same intensity are observed at δ 30.48 and 30.58 p.p.m. and two more, much less intense signals, and of approximately equal intensity, are observed at δ 35.36 and 35.48 p.p.m. Taking into consideration the higher steric compression of C-3 for the E-isomer, the two major signals at higher fields may be assigned to this isomer.

The substitution of the methylene bridge for an oxygen atom allows the assignment of practically all the signals in the ¹H and ¹³C n.m.r. spectra (see Experimental section). It should be pointed out that for imine (3c), derived from oxanorbornen-7-one and benzylamine, one isomer exclusively is observed in the ¹H n.m.r. spectrum. Thus, the benzylic H-2′ signal appears as a singlet at δ 4.42. The remaining signals of the spectrum may be assigned to one isomer as well. However, some relevant

Table 2. Relative energy (kcal mol⁻¹), population (%), and $E:Z$ ratio calculated by MM2 for products (4) and (5)

| Product	Configuration	Relative energy (kcal mol⁻¹)	Population (%)	$E:Z$ ratio
(4a)	E	0.00	66.3	2.0
	Z	0.40	33.7	
(4b)	E	0.00	58.2	1.4
	Z	0.29	41.8	
(5a)	E	0.00	65.9	1.9
	Z	0.39	34.1	
(5b)	E	0.00	60.0	1.5
	Z	0.24	40.0	

signals are duplicated in the ¹³C n.m.r. spectrum; this indicates the minor presence of a second isomer. Thus, C-1 appears as two singlets, a very intense one at δ 82.12 p.p.m. and a much less intense one at δ 76.30 p.p.m. Signals attributable to C-3 appear as two singlets, a more intense one at δ 29.78 p.p.m. and a much less intense one at δ 33.33 p.p.m. Finally, the benzylic carbon appears as two signals, a more intense one at δ 58.93 p.p.m. and a less intense one at δ 57.93 p.p.m. Considering the previous comments about differential shielding for both isomers, the major isomer can be assigned as the E-isomer.

In the case of imine (3d) derived from 1-phenylethylamine the situation is similar. In the ¹H n.m.r. spectrum, H-2′ appears as four quartets. Two major ones, very close to each other and in 1:1 ratio, are at δ 4.27 and 4.29 and two minor ones, also in 1:1 ratio are at δ 4.63. The doublets assigned to both methyl groups also appear as two pairs. One of them, of higher intensity, with both doublets at δ 1.41 and 1.49 and a less intense one with both doublets at δ 1.39 and 1.55. The isomeric ratio is ca. 10:1. The ¹³C n.m.r. spectrum is significant too in this case. The methyl group of the 1-phenylethyl moiety gave two signals of higher intensity at δ 27.73 and 24.14 p.p.m. and two signals of lower intensity at δ 24.94 and 25.36 p.p.m. The methine carbon (C-2′) also appears as two pairs of signals; a pair of higher intensity, at δ 63.44 and 63.53 p.p.m., and two less intense signals at δ 62.47 and 62.59 p.p.m. Finally, a new group of four signals with the

same distribution of intensities can be assigned to C-3. The more intense ones appear at δ 29.09 and 29.19 p.p.m. and the less intense ones at δ 33.00 and 33.20 p.p.m. Again, as in the previous discussion, the major isomer has the E configuration.

An explanation of the preference for the E-isomer as well as in the norbornane analogues[4] has been attempted by means of molecular mechanics (MM) calculations (MM2 program[5]) on model compounds.

MM2 calculations performed on ethylidene analogues of (3), [(4) and (5)] (Scheme 3) led to the results shown in Table 2. In

(4a) X = CH₂
(4b) X = O

(5a) X = CH₂
(5b) X = O
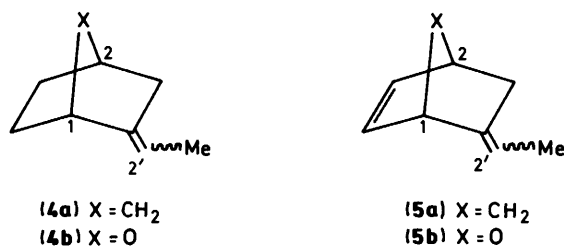
Scheme 3.

all cases, the E-isomer is the most stable thermodynamically. It may also be observed that the substitution of a 7-methylene group by an oxygen atom in the norbornene framework produces a decrease of the energy difference between the E and Z isomers, which is reflected in the calculated $E:Z$ ratio [2.0 and 1.4 for (4a and b), and 1.9 and 1.5 for (5a and b), respectively].

A detailed analysis of the geometry of compounds (4) and (5) calculated by MM2 indicates that the planarity of the H–C(1)–C(2)=C–Me moiety is the main factor responsible for the different stability of both isomers. Indeed, in the Z-isomer the methyl group interacts with H-1, giving rise to the $A^{1,3}$ allylic strain[6] between Me–H (evaluated as 0.71 kcal mol⁻¹ for a cyclohexane system[7]). The E-isomers also have Me/H $A^{1,3}$ interactions with the hydrogens at C-3; however, these are energetically smaller as a consequence of the lack of coplanarity of the groups that interact * (Scheme 4).
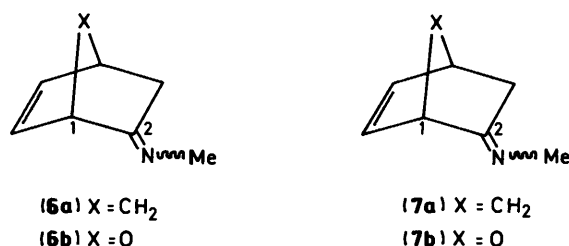

Scheme 4.

MM calculations carried out on these model systems allow for the qualitative explanation of why the E isomer always predominates over the Z. However, it is not possible to derive quantitative conclusions since (3) has a nitrogen atom in position 8. Fortunately, Allinger[8] has established the provisional parameters for different types of nitrogen atoms (sp^2). In this report, we have considered that the nitrogen atom of the Schiff's bases is equivalent to the azo type (=N–) whose parameter was established by Allinger. In spite of this, it was still necessary to define some constants of the torsion function which, provisonally too, we have assigned as $v_1 = v_2 = v_3 = 0.0$ in all cases. The results of the MM2 calculations performed on the

* For example, the angles formed by the N(1)–C(1)–C(2) and C(1)–C(2)···H(8) planes and by H(3)–C(3)–C(2) and C(1)–C(2)···Me planes for the E-isomer of (4a) are 21.6 and −65.4°, respectively.

Table 3. Relative energy (kcal mol⁻¹), population (%), and $E:Z$ ratio calculated by MM2 for products (6) and (7)

Product	Configuration	Relative energy (kcal mol⁻¹)	Population (%)	$E:Z$ ratio
(6a)	E	0.00	61.2	1.6
	Z	0.27	38.8	
(6b)	E	0.00	62.4	1.7
	Z	0.30	37.6	
(7a)	E	0.00	62.8	1.7
	Z	0.31	37.2	
(7b)	E	0.00	64.0	1.8
	Z	0.34	36.0	

Schiff's bases derived from (1) and methylamine [(6a,b) and (7a,b)] (Scheme 5) are shown in Table 3.

(6a) X = CH₂
(6b) X = O

(7a) X = CH₂
(7b) X = O

Scheme 5.

Once again the E-isomer is the more stable in all cases, although now the difference $Z - E$ is smaller. Curiously, in both (6) and (7), the substitution of CH₂ by oxygen implies an increase of the selectivity of the reaction as can be seen from the calculated $E:Z$ ratio (column 5, Table 3). The substitution of methylene by oxygen produces a shortening of the C(1)–X(7) bond [1.539 Å for (6a) and 1.418 Å for (6b)] which produces an upwards shift of 1-H (and 4-H) and this translates into a larger dihedral angle H(1)–C(1)–C(2)=N– [24° for (6a) and 31° for (6b)]. Consequently, the distance H(1)··· Me for the Z-isomers is 2.66 Å for (6a) and 2.72 Å for (6b), which brings about a decrease of stability for the Z-isomer in series a.

On the other hand, the same phenomenon occurs for the E-isomers but destabilizing interactions take place between C-3 and Me and no substantial geometrical changes between both positions are observed. The effect of the combination of these facts is an increase of the instability of the Z- with respect to the E-isomers for compounds (6) and (7). The longer C=C bond with respect to C=N causes this effect to be not so marked for (4) and (5).

The qualitative theoretical justification of the predominance of the E-isomer in the compounds considered may be found in allylic interactions of the $A^{1,3}$ type, although it seems clear that steric criteria alone are not capable of fully reproducing the observed isomeric ratios. The explanation of this fact, which has already been pointed out for open-chain azomethinic compounds,[1c] should reside in the nature of the condensation process as well as in the high energy barrier for interconversion of E- and Z-isomers[1c] which implies that the experimentally observed ratio of isomers is a consequence mainly of the kinetic control of the reaction and not of the thermodynamic stability of the isomers.

Experimental

spectrophotometer. ^{1}H N.m.r. spectra were measured on Bruker WP80SY (80 MHz) and Varian XI 200 (200 MHz) instruments. ^{13}C N.m.r. spectra were measured on Varian FT80A and on Bruker WP80SY spectrometers (20 MHz). Benzylamine and 1-phenylethylamine (Merck) were distilled prior to use. Starting materials were prepared by previously described methods; for the synthesis of norbornenone, see ref. 9, and for the synthesis of 7-oxanorbornenone, see ref. 10. MM calculations were performed on a Vax-11/785 computer in the Centro de Cálculo, of Universidad Autónoma de Barcelona.

General Method for the Preparation of Azomethines.—A 100 ml round-bottomed flask fitted with a reflux condenser and a Dean–Stark water separator was charged with ketone (1.0 g) dissolved in benzene, an equimolar amount of the corresponding amine, and a catalytic amount of the complex $ZnCl_2$–1-phenylethylamine. The solution was heated at reflux until the reaction was complete. The catalyst was removed by filtration and the solvent removed *in vacuo*.

N-*Benzylbicyclo*[2.2.1]*hept-5-en-2-ylimine* (**3a**). Reaction time, 60 min, b.p. 104 °C at 0.4 mmHg, yield 93%, $\nu_{max.}$ (CHCl$_3$) 1 685 cm^{-1} (C=N); δ_H (CDCl$_3$) 7.2 (5 H, m, Ph), 6.4—6.1 (2 H, m, 5-, 6-H), 4.60 (2 H, s, 2'-H, Z-isomer), 4.40 (2 H, s, 2'-H, E-isomer), 3.3—2.9 (2 H, m, 1-, 4-H), and 2.3—1.6 (4 H, m, 3-, 7-H); δ_C(CDCl$_3$) 178.6 (2-C), 139.4 (5-C), 133.1 (6-C), 139.8, 128.1, 127.5, 126.3 (Ph), 57.9 (2'-C, E-isomer), 57.3 (2'-C, Z-isomer), 52.7 (1-C), 50.1 (7-C), 40.7 (4-C), 35.8 (3-C, Z-isomer), and 31.4 (3-C, E-isomer) p.p.m. (Found: C, 85.4; H, 7.8; N, 7.25. C$_{14}$H$_{15}$N requires C, 85.2; H, 7.7; N, 7.1%).

N-(1-*Phenylethyl*)*bicyclo*[2.2.1]*hept-5-en-2-ylimine* (**3b**). Reaction time, 70 min, b.p. 120 °C at 0.5 mmHg, yield 98%, $\nu_{max.}$(CHCl$_3$) 1 685 cm^{-1} (C=N); δ_H(CDCl$_3$) 7.2 (5 H, m, Ph), 6.4—6.0 (2 H, m, 5-, 6-H), 4.68 and 4.65 (1 H, 2 × q, 2'-H, Z-isomer), 4.33 and 4.30 (1 H, 2 × q, 2'-H, E-isomer), 3.2 (1 H, m, 4-H), 3.0 (1 H, m, 1-H), 2.4—1.6 (4 H, m, 3-, 7-H), 1.52 (3 H, d, CH$_3$, Z-isomer), 1.48 (3 H, d, CH$_3$, E-isomer), 1.39 (3 H, d, CH$_3$, E-isomer), and 1.36 (3 H, d, CH$_3$, Z-isomer); δ_C(CDCl$_3$) 175.5 (2-C, E-isomer), 175.4 (2-C, Z-isomer), 139.9 and 139.5 (5-C, Z-isomer), 138.9 and 138.8 (5-C, E-isomer), 132.8 and 132.6 (6-C, E-isomer), 145.8, 145.6, 145.3, 144.9, 127.7, 127.6, 126.0, 125.9, 125.1 (Ph), 62.1 and 61.7 (2'-C, E-isomer), 61.3 (2'-C, Z-isomer), 52.4 (1-C), 49.5 and 49.4 (7-C), 40.3 (4-C), 35.5 and 35.4 (3-C, Z-isomer), 30.6 and 30.5 (3-C, E-isomer), 24.7 and 24.5 (CH$_3$, Z-isomer), and 23.4 and 23.7 (CH$_3$, E-isomer) p.p.m. (Found: C, 85.3; H, 8.3; N, 6.85. C$_{15}$H$_{17}$N requires C, 85; H, 8.1; N, 6.6%).

N-*Benzyl*-7-*oxabicyclo*[2.2.1]*hept-5-en-2-ylamine* (**3c**). Reaction time, 5 h, b.p. 144 °C at 0.5 mmHg, yield 98%, $\nu_{max.}$(CHCl$_3$) 1 695 cm^{-1} (C=N); δ_H(CDCl$_3$) 7.28 (5 H, s, Ph), 6.5 (2 H, m, 5-, 6-H), 5.30 (1 H, d, $J_{4,3\,exo}$ 4.20 Hz, 4-H), 4.94 (1 H, s, 1-H), 4.43 (2 H, s, 2'-H), 2.39 and 2.31 (1 H, dd, J 14.8, 15.7 Hz, 3 *exo*-H), and 2.03 and 1.80 (1 H, q, J, 14.8, 15.7 Hz, 3 *endo*-H), the AB system formed by 3 *exo*- and 3 *endo*-H was resolved by

irradiation of δ 5.30; δ_C(CDCl$_3$) 171.8 (2-C), 138.8 (5-C), 133.2 (6-C), 139.3, 128.4, 127.6, 126.8 (Ph), 82.1 (1-C, E-isomer), 78.7 (4-C), 76.3 (1-C, Z-isomer), 58.9 (2'-C, E-isomer), 57.9 (2'-C, Z-isomer), 33.3 (3-C, Z-isomer), and 29.8 (3-C, E-isomer) p.p.m. (Found: C, 78.5; H, 6.4; N, 7.3. C$_{13}$H$_{13}$NO requires C, 78.4; H, N, 7.0%).

N-(1-*Phenylethyl*)-7-*oxabicyclo*[2.2.1]*hept-5-en-2-ylimine* (**3d**). Reaction time, 5 h, b.p. 95 °C at 0.01 mmHg, yield 98%, $\nu_{max.}$(CHCl$_3$) 1 690 cm^{-1} (C=N); δ_H(CDCl$_3$) 7.3 (5 H, m, Ar), 6.5 (1 H, m, 5-H), 6.4 (1 H, m, 6-H), 5.2 (1 H, d, $J_{4,3\,exo}$ 4.0 Hz, 4-H), 4.92 (1 H, s, 1-H), 4.63 (1 H, q, 2'-H, Z-isomer), 4.29 and 4.27 (1 H, 2 × q, 2'-H, E-isomer), 2.61—1.8 (2 H, m, 3-H), 1.55 (3 H, d, CH$_3$, Z-isomer), 1.49 (3 H, d, CH$_3$, E-isomer), 1.41 (3 H, d, CH$_3$, E-isomer), and 1.39 (3 H, d, CH$_3$, Z-isomer); δ_C(CDCl$_3$) 169.3 and 169.2 (2-C, E-isomer), 138.6 and 138.5 (5-C), 133.1 and 132.8 (6-C), 144.7, 128.2, 126.6, 126.5, 126.3, 126.2 (Ph), 82.0 (1-C), 78.6 (4-C), 63.6 and 63.4 (2'-C, E-isomer), 62.6 and 62.5 (2'-C, Z-isomer), 33.2 and 33.0 (3-C, Z-isomer), 29.2 and 29.1 (3-C, E-isomer), 25.4 and 24.9 (CH$_3$, Z-isomer), and 24.1 and 23.7 (CH$_3$, E-isomer) p.p.m. (Found: C, 78.6; H, 7.2; N, 6.5. C$_{14}$H$_{15}$NO requires C, 78.8; H, 7.1; N, 6.6%).

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