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Syntheses of 6,6a,7,8,9,10,10a,11-Octahydro-11-oxodibenz[*b*,*e*]oxepins and 6,6a,7,8,9,10,10a,11-Octahydro-11-oxodibenzo[*b*,*e*]thiepins

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Two new partially saturated tricyclic ring systems, 6,6a,7,8,9,10,10a,11-octahydro-11-oxodibenz[*b*,*e*]oxepins (**3a** and **3b**), and -thiepins (**4a** and **4b**) were synthesized. Compounds **4a** and **4b** were desulfurized to give a pair of isomeric 2-methylbenzoylcyclohexanes (**10a** and **10b**). Deuterated **4a** and **4b** (**11a** and **11b**) were prepared starting from butadiene-d_6 (**12**).

The stereochemical features of **3a** (*trans*), **3b** (*cis*), **4a** (*trans*) and **4b** (*cis*) are compared with those of **10a**, **10b**, **11a** and **11b** on the basis of proton nuclear magnetic resonance data.

Keywords——6,6a,7,8,9,10,10a,11-octahydro-11-oxodibenz[*b*,*e*]oxepin; 6,6a,7,8,9,10,10a,11-octahydro-11-oxodibenz[*b*,*e*]thiepin; 2-methylbenzoylcyclohexane; deuterated 6,6a,7,8,9,10,-10a,11-octahydro-11-oxodibenz[*b*,*e*]thiepin; stereochemistry; isomerization

Compounds which have 6,11-dihydro-11-oxodibenz[*b*,*e*]oxepin (**1**) or -thiepin (**2**) ring systems have been actively investigated, because of their interesting biological activities, such as psychotropic[1] or anti-inflammatory[2] activities. However, no attention has yet been devoted to their partially reduced analogues, 6,6a,7,8,9,10,10a,11-octahydro-11-oxodibenz[*b*,*e*]oxepin (**3**) and -thiepin (**4**). Recently, Grunewald, *et al.*[3] reported that the reduction of one or both of the benzene rings of imipramine or desipramin did not cause any significant reduction of their biological activities. These facts provided the rationale for the investigation of derivatives of **3** and **4**.

As the first step in the investigation of these new tricyclic ring systems, unsubstituted **3** and **4** were synthesized to determine the chemical properties of these ring systems. The saturation of one benzene ring of **1** or **2** causes the formation of two asymmetric centers (C-6a, and C-10a) in the molecules and afforded two possible stereo-isomers (*cis*- and *trans*-isomers). The elucidation of the stereo-structures of these compounds is also covered in this paper.

Compounds **3** and **4** were synthesized as shown in Chart 1. When *cis*-hexahydrophthalide (**5**)[4] was reacted with sodium phenolate (**6**) at 225 °C, 2-(phenoxymethyl)cyclohexane carboxylic acid (**7**) was obtained. With polyphosphoric acid, **7** was cyclized to give **3** in 42% yield based on **6**. The product **3** gave two spots on thin-layer chromatography, and gas chromatography showed that it was composed of 88% of **3a** and 12% of **3b**. The mixture of the isomers **3a** and **3b** was separated on a column of silica gel eluted with *n*-hexane and toluene (95 : 5).

The reaction of **5** with thiophenol (**8**) in the presence of potassium carbonate in boiling dimethylformamide gave 2-(phenylthiomethyl)cyclohexane carboxylic acid (**9**), which was cyclized with polyphosphoric acid to afford a mixture of **4a** (95%) and **4b** (5%). It was suggested that **3a** and **3b**, and **4a** and **4b** were pairs of stereo-isomers from their infrared (IR), mass and proton nuclear magnetic resonance (^{1}H-NMR) spectral data, but these data were not considered sufficiently informative to assign the corresponding structures.

Therefore, **4a** and **4b** were desulfurized with Raney-nickel to give **10a** and **10b**,

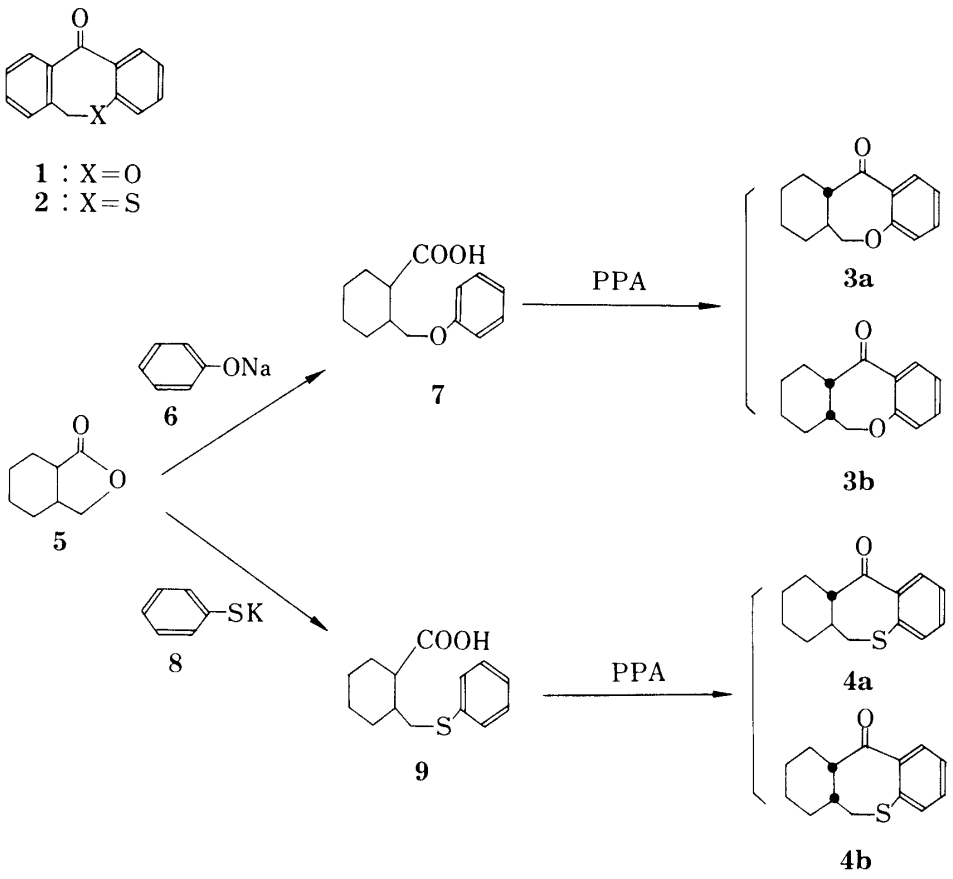


Chart 1

respectively. Comparisons of their IR and mass spectra showed that **10a** and **10b** were a pair of isomeric 2-methylbenzoylcyclohexanes.[5] Assignment of stereochemistry to the isomers, **10a** and **10b**, was readily accomplished from the ^{1}H-NMR spectra by analysis of coupling constants.[6] One of the isomers **10a** showed a multiplet for H_a (see Chart 2) at δ 3.04 and the coupling constant between H_a and H_b was 11.0 Hz; therefore, **10a** was assigned as the *trans*-isomer. On the other hand, the other isomer **10b** was assigned as the *cis*-isomer from its coupling constant between H_a and H_b (J_{ab}=4 Hz). Since the coupling constants between H_a and H_c of **10a** and **10b** were 3—4 Hz, and those between H_a and H_d were 9—10 Hz, the configurations of the benzoyl groups in **10a** and **10b** were assigned to be equatorial. From these results, **4a** was assigned as the *trans*-isomer and **4b** as the *cis*-isomer. By analogy, **3a** was assigned as the *trans*-isomer and **3b** as the *cis*-isomer.

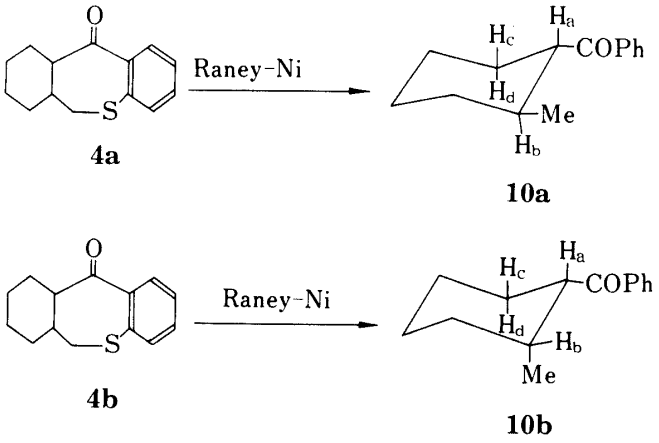


Chart 2

In order to obtain further information on **4a** and **4b**, the deuterated analogues **11a** and **11b** were prepared starting from butadiene-d_6 (**12**). The Diels–Alder cyclic addition[7] of **12** and maleic anhydride (**13**) afforded *cis*-1,2,5,6-tetrahydrophthalic anhydride-d_6 (**14**), which was reduced on palladiumcharcoal to hexahydrophthalic anhydride-d_6 (**15**).[8] The further reduction of **15** with sodium borohydride[4] gave *cis*-hexahydrophthalide-d_6 (**16**) in 65% yield. From **16**, **11a** and **11b** were prepared by the method described above.

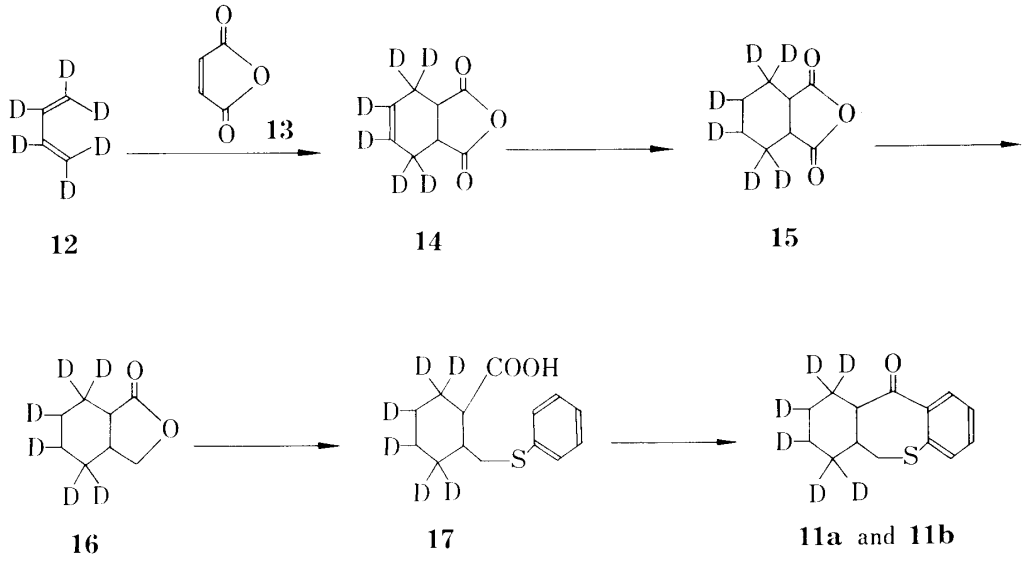


Chart 3

In the ^{1}H-NMR spectra, the signals of the bridgehead hydrogens (H_a, see Table I) of **11a** (*trans*-isomer) and **11b** (the *cis*-isomer) appeared at δ 2.29 ppm (J_{ab} = 10.4 Hz) and δ 3.51 ppm (J_{ab} = 5.8 Hz), each as doublet, respectively. Chemical shifts and coupling constants for these compounds are summarized in Table I. The assignments of chemical shifts and coupling constants for **3a**, **3b**, **4a** and **4b** were made on the basis of measured values and comparisons with those of **11a** and **11b**. Chemical shifts of the carbons of **3a**, **3b**, **4a** and **4b** were assigned by comparison of their carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectra and are also summarized in Table II.

Analogously, starting from *trans*-hexahydrophthalide in place of **5**, a mixture of **4a** and **4b** was obtained, with the *trans*-isomer **4a** predominating (**4a** : **4b** = 95 : 5).

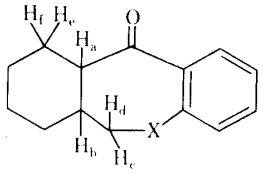
In alkaline solution, **3a**, **3b**, **4a** or **4b** gave mixtures of isomers. The mechanism of isomerization may involve protonation of the 11-oxo group to form the enol. The isomerization between **3a** and **3b**, or **4a** and **4b** in alkaline solution was investigated. The preliminary examination showed that the rate of isomerization was first-order with respect to the substrate at a constant alkali concentration. Under the conditions used for the rate measurements, no side-reaction was detected by gas chromatography and the total areas of peaks of isomers were nearly constant throughout the course of the measurement.

Equilibrium constants (k = [*cis*]/[*trans*]) estimated from the ratio of isomers at infinite reaction time were 4.83 for **3** and 16.4 for **4** at 40 °C, and were fairly well correlated to temperature (T) from 0 to 80 °C by the following equations:

$$\ln k_{3b/3a} = \ln 4.83 + 5.32 \times 10^2 \left(\frac{1}{T} - \frac{1}{313}\right)$$

$$\ln k_{4b/4a} = \ln 16.4 + 1.04 \times 10^3 \left(\frac{1}{T} - \frac{1}{313}\right)$$

TABLE I. ^{1}H-NMR Data for 6,6a,7,8,9,10,10a,11-Octahydro-11-oxodibenz[*b*, *e*]oxepins (**3**), and -Thiepins (**4** and **11**)



Compound	X	*cis*- or *trans*-	Chemical shifts (δ, ppm)				Coupling constants (Hz)			
			H_a	H_b	H_c	H_d	J_{ab}	J_{bc}	J_{bd}	J_{cd}
11a	S	*trans*	2.92 d	1.57 m	2.60 dd	2.20 dd	10.4	5.6	1.1	15.0
4a	S	*trans*	2.94[b] m	1.57 m	2.60 dd	2.20 dd	11.0	5.0	—	14.7
3a	O	*trans*	2.49[c] m	1.3 m	3.76 dd	3.57 dd	10.6	4.2	1.0	12.3
11b	S	*cis*	3.51 d	1.75 m	2.52 dd	1.98 dd	5.8	4.8	13.2	13.2
4b	S	*cis*	3.53[d] t	1.75 m	2.51 m	1.98 m	*ca.* 5	*f*)	*f*)	*f*)
3b	O	*cis*	3.00[e] t	2.1 m	4.11 dd	3.06 t	5.7	6.8	12.0	12.2

a) Run at 100 MHz in C_6D_6 with Me_4Si as an internal standard. Symbols are as follows: d, doublet; t, triplet; m, multiplet.
b) $J_{ae}=3.0$ Hz, $J_{af}=9.7$ Hz.
c) $J_{ae}=5.6$ Hz, $J_{af}=8.4$ Hz.
d) J_{ae} or $J_{af}=5.0$ Hz.
e) J_{ae} or $J_{af}=5.7$ Hz.
f) Coupling constants were not determined.

Observed isomerization rate and activation parameters in alkaline solution are given in Table III.

Experimental

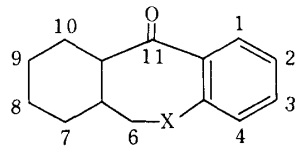
All melting points were determined with a Yanagimoto melting point apparatus and are uncorrected. ^{1}H-NMR spectra were obtained on a Varian HA-100D spectrometer and ^{13}C-NMR spectra on a Varian FT-80A spectrometer. IR spectra were recorded on a Hitachi EPI-G_3 grating infrared spectrophotometer and mass spectra on JEOL JMS D-300 mass spectrometer with an EI-CI dual ion source. High-resolution mass spectra were obtained on the same apparatus at a resolution of 5000. Solvents were removed with a rotatory evaporator under reduced pressure.

2-(Phenoxymethyl)cyclohexane Carboxylic Acid (7)——A stirred mixture of *cis*-hexahydrophthalide (**5**)[4] (18.2 g, 0.13 mol) and sodium phenolate (**6**) (11.6 g, 0.10 mol) was heated at 225 °C for 1 h and then cooled. The mixture was dissolved in H_2O and the aq solution was washed with AcOEt, acidified with 2 N HCl and extracted with toluene. The extract was evaporated to give crude **7** (21 g, 90%) as an oil: IR ν_{max}^{film} cm^{-1}: 3030—2500, 1690, 1590; MS *m/z* 234 (M^+).

***trans*- and *cis*-6,6a,7,8,9,10,10a,11-Octahydro-11-oxodibenz[*b*,*e*]oxepin (3a and 3b)**——A mixture of **7** (10.5 g, 0.045 mol) and polyphosphoric acid (PPA) (105 ml) was heated at 100 °C for 2 h and then poured into H_2O. The aq solution was extracted with toluene. The extract was washed with H_2O and evaporated to give a mixture of **3a** and **3b** (9.6 g). Analysis of the mixture by capillary gas chromatography (GC), using a methylsilicon fluid column, (12 m × 0.2 mm i.d., at 195 °C) indicated that the mixture consisted of 88% **3a** and 12% **3b**.

The separation of **3a** and **3b** was achieved by column chromatography on SiO_2 using *n*-hexane–toluene (95 : 5) as the eluent. The first fraction gave **3b** (0.5 g, 5.3%), which was recrystallized from *n*-hexane: mp 78—79 °C; IR ν_{max}^{KBr} cm^{-1}: 1675, 1597; MS *m/z* 216 (M^+); *Anal.* Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.45. Found: C, 77.67; H, 7.75.

TABLE II. ^{13}C-NMR Data for 6,6a,7,8,9,10,10a,11-Octahydro-11-oxo-dibenz[*b*, *e*]oxepins (**3**) and -Thiepins (**4** and **11**)



Carbon	*trans*			*cis*		
	3a	**4a**	**11a**	**3b**	**4b**	**11b**
1	129.3	130.4	130.4	129.4	130.4	130.4
2	122.3	125.5	125.5	122.1	125.5	125.5
3	133.1	130.4	130.4	133.0	130.4	130.4
4	120.2	129.6	129.6	119.9	129.6	129.5
4a	163.8	137.6	137.6	163.9	138.3	138.3
6	79.2	41.6	41.7	78.9	41.1	41.1
6a	45.8	46.7	46.5	42.0	45.9	45.7
7	32.6	31.2	—	26.2	29.0	—
8	26.1	25.7	25.0	24.8	25.6	24.8
9	24.9	24.8	24.0	22.8	22.6	21.9
10	26.3	26.4	—	25.8	27.6	—
10a	53.9	52.8	52.6	47.9	46.2	46.0
11	201.7	204.5	204.7	201.6	204.8	204.8
11a	128.9	142.9	143.0	128.9	142.9	142.8

TABLE III. Activation Parameters for the Isomerizations of **3** and **4** Catalyzed by NaOH (0.25 N) in 50% Dioxane

T °C	**3a**→**3b**	**3b**→**3a**	**4a**→**4b**	**4b**→**4a**
	$k_{obs} \times 10^3$/min		$k_{obs} \times 10^3$/min	
25	0.0429	0.227	0.0188	0.370
37	0.124	0.616	0.0737	1.19
50	0.402	1.86	0.287	4.27
62	1.16	5.06	0.877	11.8
Ea/kcal mol^{-1}	17.7	16.7	20.6	18.6
$\Delta S^{\neq}$/cal mol K^{-1}	−21.1	−21.4	−22.1	−22.8

The second fraction gave **3a** (4.0 g, 41.3%) which was recrystallized from *n*-hexane: mp 65—66 °C; IR ν_{max}^{KBr} cm^{-1}: 1679, 1600; MS *m/z* 216 (M^+); *Anal.* Found: C, 77.50; H, 7.45.

2-(Phenylthiomethyl)cyclohexane Carboxylic Acid (9)——A mixture of **5** (20 g, 0.14 mol) and **8** (11 g, 0.10 mol) in dimethylformamide (DMF) (100 ml) was heated at reflux temperature for 5 h. The solution was concentrated to remove DMF, followed by work-up in the same manner as described for the preparation of **7** to give crude **9** (25 g) as an oil: IR ν_{nujol}^{Im} cm^{-1} 3050—2500, 1690, 1580; MS *m/z* 250 (M^+).

***trans*- and *cis*-6,6a,7,8,9,10,10a,11-Octahydro-11-oxodibenzo[*b*,*e*]thiepin (4a and 4b)**——A mixture of **9** (25 g, 0.10 mol) and PPA (150 ml) was heated at 110 °C for 4 h, followed by work-up in the same manner as described for the preparation of **3** to give a mixture of **4a** and **4b** (22 g, 95% of **4a** and 5% of **4b**).

The mixture was chromatographed on an SiO_2 column using *n*-hexane–toluene (95 : 5) as the eluent. The first fraction gave **4b** (1.0 g, 4.3%), which was recrystallized from *n*-hexane: mp 68—69 °C: IR ν_{max}^{KBr} cm^{-1} 1667, 1583; MS *m/z* 232 (M^+). *Anal.* Calcd for $C_{14}H_{16}OS$: C, 72.37; H, 6.94; S, 13.80. Found: C, 72.37; H, 6.94; S, 13.55.

The second fraction gave **4a** (17.3 g, 74.6%), which was recrystallized from *n*-hexane: mp 98—99 °C; IR ν_{max}^{KBr} cm^{-1} 1670, 1588; MS *m/z* 232 (M^+). *Anal.* Found: C, 72.51; H, 7.13; S, 13.54.

***trans*-2-Methylbenzoylcyclohexane (10a)**——A mixture of **4a** (50 mg) and Raney-Ni (W-1) (500 mg) in MeOH (15 ml) was stirred under reflux for 1 h. The catalyst was removed, then the filtrate was evaporated and the residue was

chromatographed on an SiO_2 column. From the toluene eluate, oily **10a** (30 mg) was obtained: IR ν_{max}^{film} cm^{-1} 2920, 2850, 1675, 1595, 1580; ^{1}H-NMR (in $CDCl_3$) δ 3.04 (m, 1, J=11, 9, 3 Hz), 0.83 (d, 3, J=6 Hz); high resolution MS (M^+) Calcd for $C_{14}H_{18}O$: 202.1356. Found: 202.1323. Capillary GC (Carbowax column 20 m × 0.28 mm i.d., at 166 °C) t_R 1.9 min.

***cis*-2-Methylbenzoylcyclohexane (10b)**——When **4b** (50 mg) was treated in the same manner as described above, **10b** (30 mg) was obtained as an oil: IR ν_{max}^{film} cm^{-1} 2920, 2850, 1675, 1595, 1580; ^{1}H-NMR (in $CDCl_3$) δ 3.47 (m, 1, J= 10, 4, 4 Hz), 0.80 (d, 3, J=7 Hz); high resolution MS (M^+) Found. 202.1363. Capillary GC (Carbowax column 20 m × 0.28 mm i.d., at 166 °C) t_R 2.1 min.

***cis*-1,2,5,6-Tetrahydrophthalic Anhydride-d_6 (14)**——A mixture of butadiene-d_6 (**12**) (2.68 g, 0.045 mol) and maleic anhydride (**13**) (4.16 g, 0.042 mol) in toluene (65 ml) was heated at 100 °C in a sealed tube for 6 h. The solvent was removed and the residue was recrystallized from toluene to give **14** (4.5 g, 67.2%): mp 100—102 °C; IR ν_{max}^{KBr} cm^{-1} 2950, 2270—2100, 1835, 1750; ^{1}H-NMR (in $CDCl_3$) δ 3.38 (s); MS (CI) m/z 159 (MH^+).

***cis*-1,2,3,4,5,6-Hexahydrophthalic Anhydride-d_6 (15)**——A solution of **14** (4.4 g, 0.028 mol) in AcOEt (50 ml) was stirred in an atmosphere of hydrogen in the presence of 5% Pd–C (0.2 g). When the theoretical amount of hydrogen had been absorbed, the catalyst was removed and the solvent was evaporated off to give crude **15** (4.4 g, 98.8%) as an oil: IR ν_{max}^{film} cm^{-1} 2930, 2200—2100, 1850, 1770; ^{1}H-NMR (in $CDCl_3$) δ 3.11 (s, 2), 1.47 (s, 2); MS (CI) m/z 161 (MH^+).

***cis*-1,2,3,4,5,6-Hexahydrophthalide-d_6 (16)**——A cold solution of sodium borohydride (1.3 g, 0.033 mol) in tetrahydrofuran (THF, 20 ml) was added over a period of 5 min, to a solution of **15** (4.4 g, 0.028 mol) in THF (920 ml). After being stirred for 30 min, 6 N HCl was added to the mixture. The whole was concentrated and the residue was extracted with toluene. The extract was evaporated to give crude **16** (3.9 g, 98.4%) as an oil: IR ν_{max}^{film} cm^{-1} 2900, 2200—2100, 1770; ^{1}H-NMR (in $CDCl_3$) δ 4.21 (dd, 1, J=9, 6 Hz), 3.95 (dd, 1, J=9, 2 Hz), 2.64 (d, 1, J=6 Hz), 2.56—2.35 (m, 1, J=9, 6, 2 Hz), 1.54 (s, 1), 1.18 (s, 1); MS (CI) m/z 147 (MH^+).

2-(Phenylthiomethyl)cyclohexane Carboxylic Acid-d_6 (17)——When **16** (3.9 g, 0.027 mol) was treated in the same manner as described for the preparation of **9**, crude **17** (5.1 g, 74.6%) was obtained as an oil: IR ν_{max}^{film} cm^{-1} 3050—2600, 2200—2100, 1696, 1580; ^{1}H-NMR (in $CDCl_3$) δ 10.50 (s, 1, exchangeable with D_2O), 7.43—7.10 (m, 5), 3.26—2.80 (m, 3), 2.12—1.90 (m, 1), 1.56—1.26 (m, 2); MS (CI) m/z 257 (MH^+).

***trans*- and *cis*-6,6a,7,8,9,10,10a,11-Octahydro-11-oxodibenzo[*b*,*e*]thiepin-d_6 (11a and 11b)**——When **17** (5.1 g, 0.020 mol) was treated in the same manner as described for the preparation of **3**, a crude mixture of **11a** and **11b** (5.0 g) was obtained. The mixture was chromatographed on SiO_2 with *n*-hexane–toluene (95 : 5) as the eluent.

The first fraction gave **11b** (0.30 g, 6.3%). Recrystallization from MeOH gave pure **11b**: mp 69—70 °C; IR ν_{max}^{KBr} cm^{-1} 3045, 2905, 2860, 2195, 2177, 2107, 1669, 1587; MS m/z 238 (83%), 237 (16%), 236 (2%), 235 (0.2%).

The second fraction afforded **11a** (4.3 g, 91%). Recrystallization from *n*-hexane gave pure **11a**: mp 97—98 °C; IR ν_{max}^{KBr} cm^{-1} 3045, 2905, 2885, 2195, 2165, 2100, 1667, 1586; MS m/z 238 (83%), 237 (16%), 236 (2%), 235 (0.2%).

Determination of Rate Constant——About 4 mg of the sample was dissolved in 20 ml of 0.25 N NaOH (in 50% dioxane) at a controlled temperature. At regular intervals 1 ml of the solution was extracted quickly with 2 ml of $CHCl_3$ and an aliquot of the organic layer was introduced into the capillary GC under the following conditions: instrument, Hewlett Packard model 5840A with 18835B capillary inlet system; column, methylsilicon fluid (WCOT, 12 m × 0.2 mm i.d.); oven temp., 300 °C; carrier gas flow (He), 1.5 ml/min ($\bar{\mu}$=34 cm/s).

Under these conditions **3a**, **3b**, **4a** and **4b** gave rise to peaks at 4.71, 4.59, 6.40 and 6.24, respectively, showing good resolution.

The sum of rate constants for the forward (k_f; *cis*→*trans*) and reverse (k_r; *trans*→*cis*) directions was estimated from the slope of a plot of $\ln(A_0-A_e)/(A_t-A_e)$ against time, where A_0, A_t and A_e represent the peak area ratios of *cis* to *trans* or *vice versa* on chromatograms at reaction time 0, time t and infinite time, respectively. A good first-order plot was obtained in every run.

Each k_f and k_r was calculated by use of the stationary-state approximation from the sum of the two and the equilibrium constant (A_e).

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