Dioxopyrrolines. XLII.[1] Mechanism of 7-Epimerization Reaction of 7-Substituted 5-Ethoxycarbonyl-1-phenyl-2-azabicyclo[3.2.0]heptane-3,4-diones

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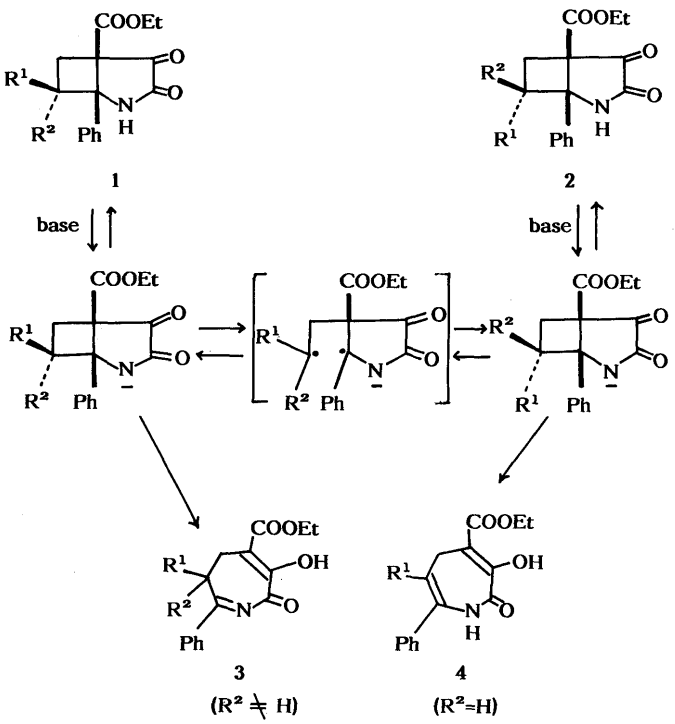
7-Mono- and 7,7-disubstituted 5-ethoxycarbonyl-1-phenyl-2-azabicyclo[3.2.0]heptane-3,4-diones undergo epimerization at C-7 when treated with base. Experiments using the stereospecifically deuterium labeled compound 6 showed that the inversion of stereochemistries at C-6 and C-7 took place simultaneously in this reaction, thus proving that the reaction proceeded through C_1–C_5 bond fission and recyclization. The suggested intermediate 10 with a highly strained seven membered ring would give either the C_7 epimerized product by a fast recombination or irreversibly give the dihydroazatropolones 9 by a *trans*- to *cis*- isomerization of the C=N double bond. Kinetic treatments showed that the latter reaction is slower than the former equilibrium reaction.

The analogous 7-epimerization reaction observed in the hydride reduction of the 4-oxo group and in the photolysis of the imidate 24 was proved to proceed with a similar mechanism.

Keywords 2-azabicyclo[3.2.0]heptane-3,4-dione; cyclobutane; deuterium label; base catalyzed epimerization; *exo–endo* epimerization; stereochemistry; mechanism; kinetics; hydride reduction; photolysis

Introduction

Previously we reported[2-3] that 7-*exo*-substituted 2-azabicyclo[3.2.0]heptane-3,4-diones **1**, on treatment with bases such as triethylamine and 1,5-diazabicyclo[5.4.0]-undec-5-ene (DBU) in benzene readily undergo epimerization of the C_7-substituent to give the thermodynamically more stable *endo*-isomers **2** exclusively. For 7,7-disubstituted derivatives an evident equilibrium was observed, since the difference of thermodynamic stability between the 7-isomers was small. Upon prolonged treatment with the bases, either **1** or **2** underwent ring expansion at the C_1–C_5 bond to irreversibly give the dihydroazatropolone (**3** for $R^2 \neq H$ or **4** for $R^2 = H$).[4] Participation of an anion species in these reactions was evidenced by the following facts: i) both reactions are greatly accelerated by increase of the basicity of the reagent (*cf.* triethylamine *vs.* DBU), ii) the *N*-methyl derivative **5** was not affected on heating with triethylamine in benzene, and iii) the compound **1a** was recovered unchanged after heating in benzene without base.



	R^1	R^2
a :	Ph	H
b :	OEt	H
c :	OAc	H
d :	Et	H
e :	Me	OAc
f :	Ph	Me

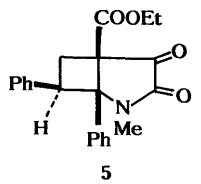


Chart 1. Previously Presented 7-Epimerization Mechanism[2]

Preliminary kinetic studies[2] indicated that the epimerization occurred far more rapidly than the dihydroazatropolone formation. Since the latter reaction is irreversible, the possibility that the epimerization proceeds by recyclization of dihydroazatropolone can obviously be eliminated. Assuming that the epimerization arises from the C_1–C_7 bond fission–recombination process, the anion-radical mechanism shown in Chart 1 was suggested,[2] although intermediacy of such an anion-radical species lacked experimental evidence.

In this paper we present the details of mechanistic studies of this epimerization reaction using stereospecifically deuterium-labeled compounds; the results revealed that the previous mechanism must be revised to a C_1–C_5 bond fission–recyclization process. The new mechanism we propose here satisfactorily explains the stereochemical course of the reaction.

Results and Discussion

Epimerization under Basic Conditions In order to clarify in detail the stereochemistry of the 7-epimerization reaction with bases we chose the 6-*exo*-deuterio-7-*exo*-phenyl derivative **6**[5] (6β-D,7β-Ph)[6] as a substrate. If the epimerization proceeds *via* the C_1–C_7 bond fission and recyclization, the resulting 7α-Ph derivative **7** should have the stereochemistry in which the 6-D configuration is retained (6β-D,7α-Ph). On the other hand, if the 7-epimerization occurs *via* the C_1–C_5 bond fission and recyclization, both

the stereochemistry at 6-D and 7-Ph would be inverted in the epimerized product **8** (6α-D,7α-Ph).[5] These two pathways are now distinguishable.

Heating of **6** in 10% triethylamine–benzene under reflux for 3 h gave the 7α-Ph derivative **8** in 50% yield. Treatment of **6** with a stronger base (2% DBU–benzene solution at room temperature) gave the dihydroazatropolone **9** in 62% yield. The proton nuclear magnetic reasonance (^{1}H-NMR) spectrum of **8** clearly indicated that this is the 6α-D derivative. The absence of contamination with the 6β-D derivative **7** was confirmed, since it gave only a doublet (J= 7 Hz) at δ 2.68 corresponding to the 6α-D,7α-Ph derivative.[5] The result clearly shows that the reaction caused the simultaneous inversion of both the 7-phenyl and 6-deuterium groups. This phenomenon can be interpreted as the result of simultaneous inversion of the 1-phenyl and 5-ethoxycarbonyl groups produced by the C_1–C_5 bond fission–recyclization process that results in the overall simultaneous turning of the 6- and 7-substituents from the *exo* to the *endo* face or *vice versa*.[7]

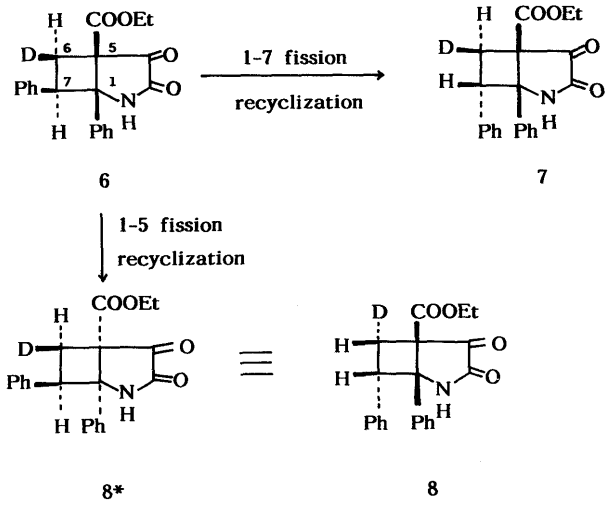


Chart 2. Differentiation of the 1–7 Process and the 1–5 Process

As mentioned above, dihydroazatropolone is not the intermediate of this epimerization reaction. The question arises, if the epimerization proceeds through the C_1–C_5 bond fission, what species is the real intermediate? We assume that the seven membered ring species **10** containing a *trans* C=N bond might be the intermediate. This highly strained species could be formed by a concerted ring opening of the anion species **11** or **12** at the C_1–C_5 bond. Ring inversion (only disrotatory movement is plausible) and recyclization (conrotatory movement facilitates this) of this highly reactive intermediate produces the double inversion of 1-Ph and 5-COOEt groups, thus resulting in the double epimerization at C_6 and C_7. On the other hand, the isomerization of the C=N double bond from *trans* to *cis* results in a great stabilization of the ring, thus leading to irreversible formation of the dihydroazatropolone **9**. Slow formation of **9** indicated that this isomerization is slower than the recombination of the C_1–C_5 bond.

Kinetic Studies The reactions with 10% triethylamine in benzene at 80 °C were subjected to time dependent product analysis. For **1b**, **2b**, **2c**, and **1d**, the curves (Fig. 1) indicated that the *exo* (A) and *endo* (B) isomers are in rapid equilibrium. The dihydroazatropolone formation was too slow to evaluate the rate constant under these conditions. It was observed only for **1d** (10% after 10 h). In these cases the

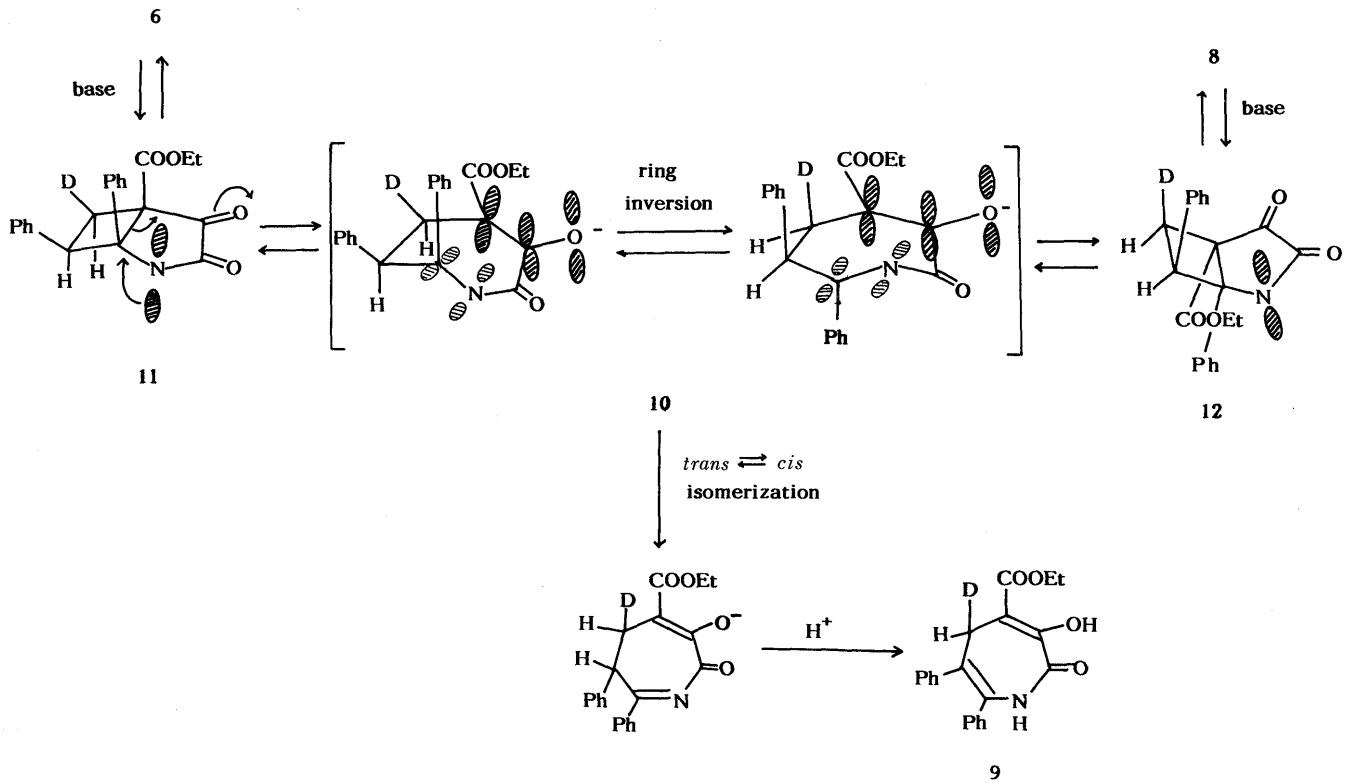


Chart 3

reaction thus appears as $A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} B$. The rate constants were roughly estimated from the curves as k_1 *ca.* $1.45\,h^{-1}$ and k_{-1} *ca.* $0.25\,h^{-1}$, thus K *ca.* 1/6.

The 7-Ph derivatives **2a** gave only B (*endo*) and C (dihydroazatropolone) as observable products, while three products, A (*exo*), B (*endo*), and C (dihydroazatropolone) were observed when the reaction was started from **1a** (Fig. 2). Thus the reaction appears as $A \overset{k_1}{\rightarrow} B \overset{k_2}{\rightarrow} C$. The rate constants roughly estimated were k_1 *ca.* $0.8\,h^{-1}$ and k_2 *ca.* $0.3\,h^{-1}$. The rate of the reverse reaction B → A was too small to evaluate from the curve.

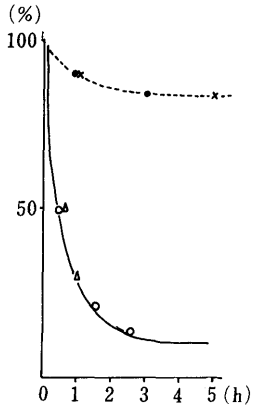


Fig. 1. Base-Catalyzed Equilibrium of **1b**, **2b**, **2c** and **1d** (Conditions: 10% NEt_3 in Benzene, 80 °C)

---×---, **2b**; ---●---, **2c**; —○—, **1b**; —△—, **1d**.

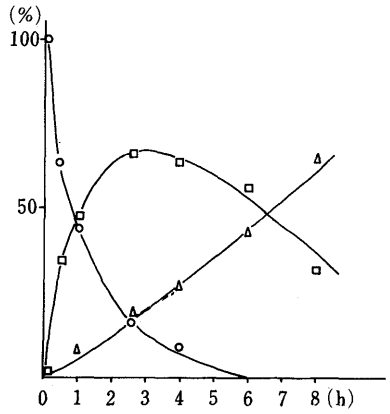


Fig. 2. Base-Catalyzed Reaction of **1a** (Conditions: 10% NEt_3 in Benzene, 80 °C)

—○—, **1a**; —□—, **2a**; —△—, **4a**.

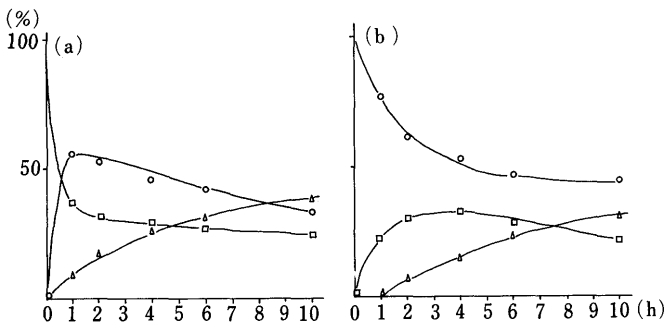


Fig. 3. Base-Catalyzed Reaction of the 7-Acetoxy-7-methyl Derivative (Conditions: 10% NEt_3 in Benzene, 80 °C)

3-a: Starting from **1e**. 3-b: Starting from **2e**. —□—, **1e**; —○—, **2e**; —△—, **3e**.

For the disubstituted derivatives (**1e** and **2e**) the results were complicated, since the stabilities of the two isomers became similar (Fig. 3a and 3b). The product curves obtained by starting from **1e** (Fig. 3a) were then analyzed by a computer using the NONLIN program[8] assuming that the reaction follows Chart 4-(a)[2] to give the rate constant of each step as $k_1' = 1.87 + 0.7\,h^{-1}$, $k_2' = 1.20 + 0.5\,h^{-1}$, $k_3' = 0.14 + 0.008\ h^{-1}$, and $k_4' = 0.4 \times 10^{-3} + 0.47 \times 10^{-3}\ h^{-1}$. Thus the equilibrium constant (K) can be roughly estimated as $k_2'/k_1' = 1/1.5$. Since Chart 4 (mechanism proposed in the present investigation) are indistinguishable in kinetic treatment, the ratio k_3'/k_4' of the apparent constants in Chart 4-(a) must roughly correspond to the ratio k_1/k_3 in Chart 4-(b). The rate of dihydroazatropolone formation (k_5) can now be roughly calculated from the decrease of the concentrations of A + B as $k_5 = 0.0045\ h^{-1}$. These results mean that the equilibrium between A and B occurs more than 40 times faster than the *trans*- to *cis*-isomerization of the intermediate.

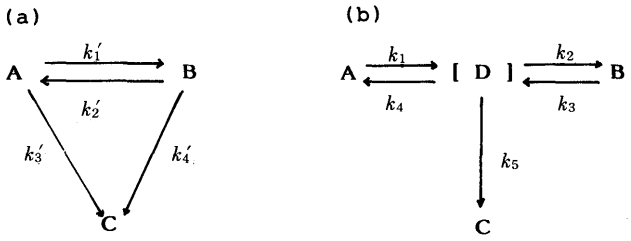


Chart 4

Epimerization in Hydride Reduction During the studies on the chemical transformation of 2-azabicyclo[3.2.0]-heptane-3,4-diones and their derivatives, we have sometimes observed a similar 7-epimerization reaction under various conditions.

Reduction of the 7β-Ph derivative **1a** with tetra-*n*-butylammonium borohydride in dichloromethane (followed by acetylation of the resulting alcohols) gave the 4β-OAc derivative **13** (60%) and the 4α-OAc isomer **14** (5%). Similar reduction of the 7α-Ph derivative **2a** (and subsequent acetylation) produced two stereoisomeric acetates **15** and **13** in yield of 61% and 25%. The major product **15** was the normal 7α-Ph, 4α-OAc derivative, while the minor product **13** was, unexpectedly, identical with the 7β-Ph, 4β-OAc derivative, the 7-epimerization product.

Reduction of the 6α-D,7α-Ph derivative **8** similarly gave two acetates, the 7α-Ph,4β-OAc compound **17** as a major product and the 7β-Ph,4β-OAc compound **16** as a minor product. In the ^{1}H-NMR spectra the C_6-H signal of **16** appeared at δ 2.92 as a doublet ($J = 9$ Hz) and that of **17** at δ 2.87 as a doublet ($J = 9$ Hz), thus showing that C_6-H in **16** and **17** occupies *endo* and *exo* positions, respectively. No contamination with the other stereoisomer was observed. Again, the simultaneous inversion of both the 7-phenyl and 6-deuterium groups took place. Reduction of the 6β-D,7β-Ph derivative **6** (and acetylation of the product) produced the acetate **16** exclusively, as expected.

The 7β-Ph,7α-Me compound **1f** on a similar hydride reduction partially underwent 7-epimerization to give the 7α-Ph, 7β-Me, 4α-OAc **20** (13%) together with the normal reduction products **18** (40%) and **19** (36%). On the other

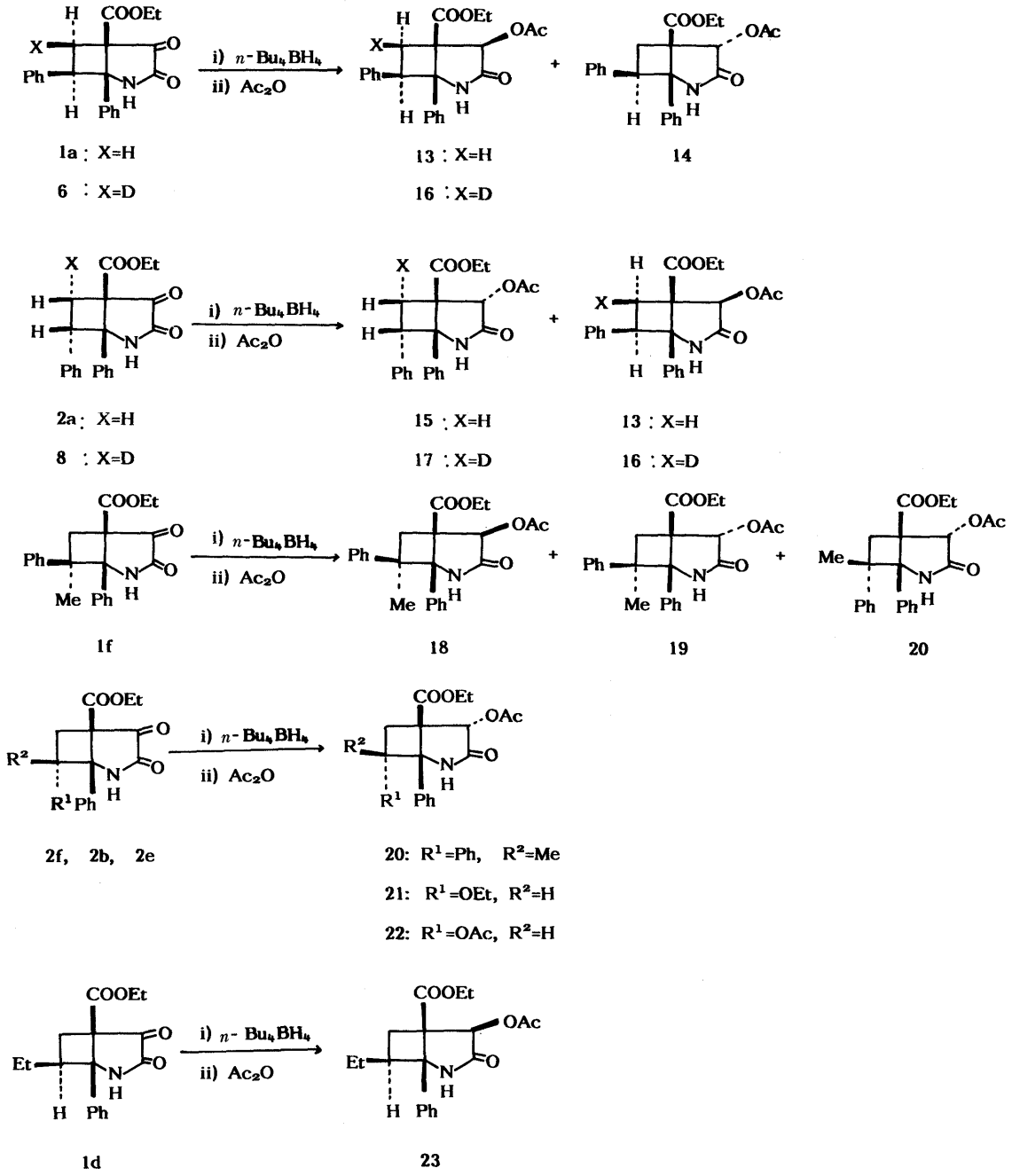


Chart 5

hand, reduction of the 7α-Ph,7β-Me isomer **2f** gave no 7-epimerization product, yielding **20** as the sole product (49%). Similar reductions of other derivatives such as **2b**, **2e** and **1d** gave the normal products **21** (64%), **22** (66%) and **23** (59%), each as a single product, respectively.

Stereochemistry of the 4-acetoxyl group in the products was elucidated on the basis of the steric compression effect[9] observed in the ^{13}C-NMR spectra. As shown in Table I, the 4α-OAc isomers exhibited the C_6-signal at higher field than that of the original 4-*oxo* derivatives,[3] while the 4β-OAc isomers gave the C_6-signal at lower field. This higher magnetic field shift observed in the 4α-OAc isomers can be attributed to the steric compression between the 4-OAc group and the 6-methylene carbon. In support of this assignment, catalytic hydrogenation of the acetylene adduct **24** gave **13** (after acetylation) as a sole product, indicating

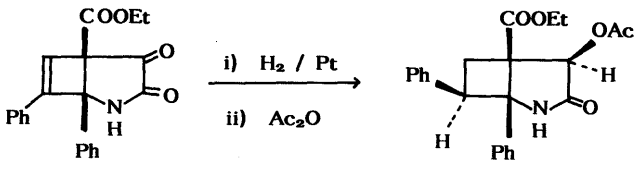


Chart 6

that 7-Ph and 4-OAc in **13** have the same orientation.

Since the reduction products (either alcohols or acetates) showed no tendency to epimerize in the presence of hydride or base, we concluded that the epimerization occurred before the reduction of the C_4-carbonyl group, *i.e.* at the 4-ketone stage, by an analogous mechanism to that discussed in the above section. The formation of the thermodynami-

cally less stable 7β-Ph derivative from the more stable 7α-Ph isomer observed in the reduction of **2a** can be explained by the faster reduction of the 4-ketone in the *exo* derivative than that in the *endo* isomer. Even if the *exo* isomer is less stable and of lesser population in the equilibrium mixture, it is more rapidly reduced to the 4-*exo*-alcohol for the steric reasons thus giving a considerable amount of the epimerization product. In fact, hydride reduction of the *endo* isomer **2a** is much slower than that of **1a**.

TABLE I. Chemical Shifts of the 6-Carbon in the ^{13}C-NMR Spectra of 4-Oxo and 4-Acetoxy Derivatives, and Stereochemical Assignment of the 4-OAc Group

Stereochemistry of 7-substituents		Chemical shifts of C_6		C_6 OAc–CO	Stereochemistry of 4-OAc
(*exo*)	(*endo*)	4-Ketone	4-Acetate		
H	Ph	24.8 (**1a**)	29.6 (**13**)	+4.8	*exo*
H	Ph	24.8 (**1a**)	21.6 (**14**)	−3.8	*endo*
Ph	H	25.3 (**2a**)	23.5 (**15**)	−2.8	*endo*
Me	Ph	35.9 (**1f**)	38.5 (**18**)	+2.7	*exo*
Me	Ph	35.9 (**1f**)	29.9 (**19**)	−6.0	*endo*
Ph	Me	33.5 (**2f**)	30.5 (**20**)	−3.0	*endo*
OEt	H	31.5 (**2b**)	28.2 (**21**)	−3.3	*endo*
OAc	Me	38.2 (**1e**)	35.8 (**22**)	−2.4	*endo*
H	Et	27.5 (**1d**)	31.6 (**23**)	+4.1	*exo*

Epimerization of the Imidate under Photochemical Conditions 2-Azabicyclo[3.2.0]heptane-3,4-diones are readily transformed to the imidates by the action of triethyloxonium fluoroborate. Photolysis of the 7β-Ph imidate **25** in dimethoxyethane using a high-pressure Hg lamp again resulted in the 7-epimerization forming the corresponding 7α-Ph derivative **26** in 50% yield. This epimerization was also proved to occur through the C_1–C_5 bond fission–recyclization process, since irradiation of the imidate **27** (6β-D,7β-Ph) again caused the simultaneous inversion of 6-D and 7-Ph to give the imidate **28** (6α-D,7α-Ph), identical with the imidate prepared by the alkylation of **8** with triethyloxonium fluoroborate, thus confirming the structure. This photo-isomerization may proceed *via* the biradical **29** formed by disrotatory ring opening of the C_1–C_5 bond and the subsequent disrotatory ring closure of **29**. The similar photolysis of the amide **1a** merely caused deterioration of the starting material.

Epimerization unde Other Conditions Besides the above reactions, similar 7-epimerization, at least partially, was observed in the following reactions, though no confirmatory mechanistic evidence was available in these cases. They are thermolysis of 7β-vinyl derivatives of 1-aryl-5-ethoxycarbonyl-2-azabicyclo[3.2.0]heptane-3,4-dione[10] and thermolysis of the imidates of 7-substituted 5-ethoxycar-

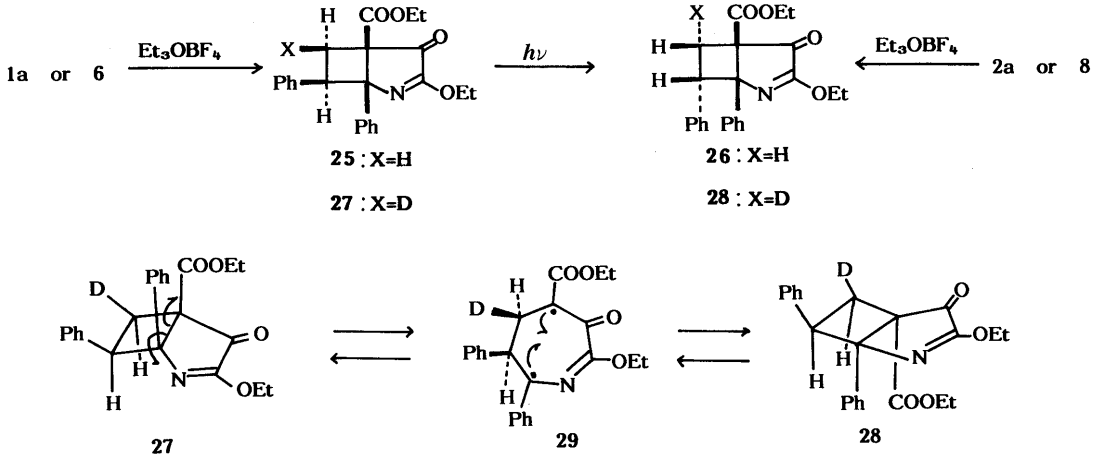


Chart 7

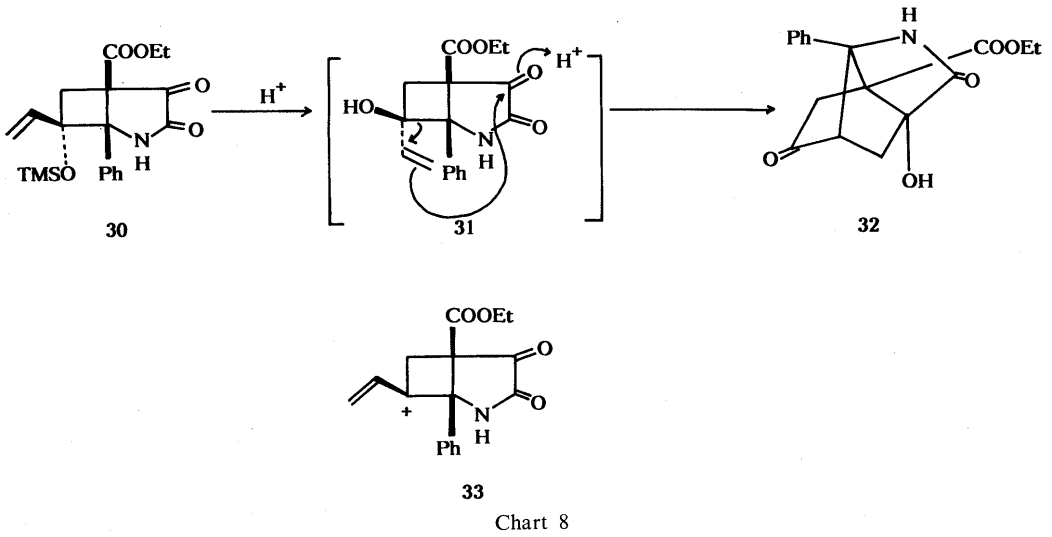


Chart 8

bonyl-1-phenyl-2-azabicyclo[3.2.0]heptane-3,4-dione.[11] In those reactions, the epimerization possibly proceeds *via* the 1—5 fission–recombination process. However, the possibility of a 1—7 fission–recombination process can not be excluded.[12]

Acidic treatment of the 7β-vinyl-7α-trimethylsilyloxy-5-ethoxycarbonyl-1-phenyl-2-azabicyclo[3.2.0]heptane-3,4-dione **30** gave the cage compound **32**, which is apparently formed from the 7α-vinyl-7β-hydroxyl derivative **31**.[13,14] The 7-epimerization in this reaction might occur through a different mechanism involving a carbocation **33**. The details of these reactions will be discussed in subsequent papers.

Experimental

Unless otherwise stated, the following procedures were adopted. Melting points were taken on a Yanagimoto micro hot-stage melting point apparatus and are uncorrected. Infrared (IR) spectra were taken in Nujol mulls for solids and as liquid films for liquids with a Hitachi 260-10 spectrometer and are given in cm^{-1}. Ultraviolet (UV) spectra were recorded in EtOH solution with a Hitachi 200-10 spectrophotometer and are given in λ_{max} nm (ε). ^{1}H-NMR (100 MHz) and ^{13}C-NMR (25.0 MHz) spectra were taken in $CDCl_3$ solution with tetramethylsilane as an internal standard on a JEOL FX-100 spectrometer, respectively. High resolution mass spectra (MS) were recorded on a JEOL JMS-D300 mass spectrometer. For column chromatography, silica gel (Wako gel C-200) was used. Thin layer chromatography (TLC) was performed on Merck precoated Silica gel 60 F_{254} plates. Medium pressure liquid chromatography (MPLC) was performed on a Kusano CIC prepacked silica gel column. Photolysis was done by external irradiation using a 300 W high-pressure mercury lamp (Eikosha Halos PIH 300) with a Pyrex filter.

2-Azabicyclo[3.2.0]heptane-3,4-diones 1, 2, 6, and 7 The cyclobutanes **1**, **2**, **6**, and **7** were reported in refs. 3 and 5.

Treatment of 6 with Triethylamine A solution of **6** (145 mg) in 10% triethylamine–benzene (30 ml) was heated under reflux for 2.5 h. The solvent was evaporated off *in vacuo* and the residue was chromatographed over SiO_2 in CH_2Cl_2 to give (1*S**,5*R**,6*S**,7*S**)-6-deuterio-5-ethoxycarbonyl-1,7-diphenyl-2-azabicyclo[3.2.0]heptane-3,4-dione **8** (73 mg, 50%), which was crystallized from CH_2Cl_2–Et_2O as colorless needles, mp 178—188 °C. IR: 3320, 1770, 1740, 1710. ^{1}H-NMR: 0.72 (3H, t, J=7 Hz, $COOCH_2\underline{CH_3}$), 3.34 (1H, d, J=9 Hz, C_6-H), 3.78 (2H, q, J=7 Hz, $COO\underline{CH_2}CH_3$), 4.82 (1H, d, J=9 Hz, C_7-H), 7.0—7.5 (10H, m, Ar-H). MS *m/z*: M^+ Calcd for $C_{21}H_{19}DNO_4$ 350.1377. Found: 350.1370.

Treatment of 6 with DBU A solution of **6** (24 mg) in 2% DBU–benzene (40 ml) was stirred at room temperature overnight. The reaction mixture was diluted with CH_2Cl_2 and washed with 5% HCl and water. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*, and the crystalline residue was chromatographed over SiO_2. Elution with CH_2Cl_2 gave 5-deuterio-4-ethoxycarbonyl-3-hydroxy-6,7-diphenyl-1,5-dihydro-2*H*-azepin-2-one **9** (150 mg, 62%) as pale yellow needles from CH_2Cl_2–Et_2O, mp 218—220 °C. IR: 3170, 1660, 1600. UV: 228 (18000), 269 (15000). ^{1}H-NMR: 1.02 (3H, t, J=7 Hz, $COOCH_2\underline{CH_3}$), 3.42 (1H, s, C_5-H), 4.11 (2H, q, J=7 Hz, $COO\underline{CH_2}CH_3$), 7.1—7.4 (10H, m, Ar-H). MS *m/z*: M^+ Calcd for $C_{21}H_{18}DNO_4$ 350.1376. Found: 350.1381.

Reactions of 1 and 2 with 10% NEt_3–Benzene Solution: Measurement of Product Ratios (Time Course) A solution of **1a**, **2a**, **1b**, **2b**, **2c**, **1d**, **1e**, or **2e** (each 100 mg) in 10 % (w/v) NEt_3–benzene (40 ml) was heated under reflux (80 °C). At appropriate intervals an aliquot of the reaction mixture was taken and, after evaporation of the solvent *in vacuo*, subjected to ^{1}H-NMR measurement. The product ratios of **1a**, **2a** and **4a**, of **1b** and **2b**, and of **1d** and **2d** were measured in therms of the intensity ratio of their corresponding methyl signals of COOEt, and those of **1c** and **2c**, and of **1e**, **2e** and **3e** were measured in therms of the intensity ratio of the methyl signal of OAc. The results are given in Figs. 1—3 and Tables II—V.

Reduction of 5-Ethoxycarbonyl-1-phenyl-2-azabicyclo[3.2.0]heptane-3,4-diones with Tetra-*n*-butylammonium Borohydride (General Procedure) A 2-azabicyclo[3.2.0]heptane-3,4-dione (100 mg) in CH_2Cl_2 (10 ml) was treated with $(n\text{-}C_4H_9)_4BH_4$ (0.5 mol eq) at 0 °C for 3—45 min. The reaction mixture was diluted with CH_2Cl_2 and washed with water, and the organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was acetylated with Ac_2O (1 ml) and pyridine (2 ml) at room temperature overnight. The acetate obtained by usual work-up was purified by MPLC using *n*-hexane–AcOEt (3 : 1) as an eluent.

Table II. Product Ratio Starting from **1a**

Time (h)	Product ratio (%)		
	1a	**2a**	**4a**
0	100	0	0
0.5	62	38	0
1	45	45	9
2.5	16.7	66.7	16.7
4	10	63	26
6	0	57	43
8	0	33	67

Table III. Product Ratio Starting from **2a**

Time (h)	Product ratio (%)		
	1a	**2a**	**4a**
0	0	100	0
0.5	0	87	13
1.5	0	50	50
3	0	17	83

Table IV. Product Ratio Starting from **1e**

Time (h)	Product ratio (%)		
	1e	**2e**	**3e**
0	100	0	0
1	36.5	56	7.5
2	31	52.5	16.5
4	29	45.5	25.5
6	27	42.5	30.5
10	25.7	35.8	38.5

Table V. Product Ratio Starting from **2e**

Time (h)	Product ratio (%)		
	1e	**2e**	**3e**
0	0	100	0
1	23	77	0
2	30	62	7
4	32	53	15
6	28	48	24
10	24	45	31

i) Reduction of **1a** (100 mg) gave **13** (68 mg, 60%) and **14** (6 mg, 5%). **13**: (1*S**,4*R**,5*R**,7*R**)-4-Acetoxy-5-ethoxycarbonyl-1,7-diphenyl-2-azabicyclo[3.2.0]heptan-3-one. Colorless needles from CH_2Cl_2–Et_2O, mp 210—214 °C. IR: 1750, 1730, 1705. UV: 260 sh (600). ^{1}H-NMR: 0.75 (3H, t, J=7 Hz, $COOCH_2\underline{CH_3}$), 2.13 (3H, s, OAc), 2.68 (1H, dd, J=10, 12 Hz, C_6-H), 3.29 (1H, dd, J=11, 12 Hz, C_6-H), 3.71 (2H, q, J=7 Hz, $COO\underline{CH_2}CH_3$), 4.16 (1H, dd, J=10, 11 Hz, C_7-H), 5.98 (1H, s, C_4-H), 6.85—7.25 (10H, m, Ar-H), 8.33 (1H, s, NH). ^{13}C-NMR: 13.6 (q, $COOCH_2\underline{C}H_3$), 2.04 (q, $OCO\underline{C}H_3$), 29.6 (t, C_6), 52.3 (d, C_7), 56.4 (s, C_5), 60.6 (t, $COO\underline{C}H_2CH_3$), 71.6 (s, C_1), 77.4 (d, C_5), 125.9 (d, 2C, Ph), 126.3 (d, Ph), 127.1 (d, 2C, Ph), 127.3 (d, Ph), 127.8 (d, 2C, Ph), 128.1 (d, 2C, Ph), 135.5 (s, Ph), 137.8 (s, Ph), 168.3 (s, C_3), 169.9 (s, $\underline{C}OOCH_2CH_3$), 173.8 (s, $O\underline{C}OCH_3$). *Anal.* Calcd for $C_{23}H_{23}NO_5$: C, 70.21; H, 5.89; N, 3.56. MS *m/z*: 393.1574. Found: C, 69.96; H, 5.96; N, 3.50. M^+ *m/z*: 393.1573. **14**: (1*S**,4*S**,5*R**,7*R**)-4-Acetoxy-5-ethoxycarbonyl-1,7-diphenyl-2-azabicyclo[3.2.0]heptan-3-one. Colorless prisms from CH_2Cl_2–Et_2O, mp 208—211 °C. IR: 1745, 1730, 1705. UV: 260 sh (600). ^{1}H-NMR: 0.75 (3H, t, J=7 Hz, $COOCH_2\underline{CH_3}$), 2.24 (3H, s, OAc), 2.50 (1H, dd, J=10, 13 Hz, C_6-H), 3.38 (1H, dd, J=11, 13 Hz, C_6-H), 3.72 (2H, q, J=7 Hz, $COO\underline{CH_2}CH_3$), 4.09 (1H, dd, J=10, 11 Hz, C_7-H), 5.82 (1H, s, C_4-H), 6.85—7.3 (10, m, Ar-H), 8.27 (1H, s, NH). ^{13}C-NMR: 13.5 (q, $COOCH_2\underline{C}H_3$), 20.3 (q, $OCO\underline{C}H_3$), 21.0 (t, C_6), 52.8 (d, C_7), 55.1 (s, C_5), 61.5 (t, $COO\underline{C}H_2CH_3$), 71.2 (s, C_1), 74.4 (d, C_4), 126.5 (d, 2C, Ph), 127.5

(d, 2C, Ph), 127.6 (d, 2C, Ph), 127.8 (d, Ph), 128.2 (d, 3C, Ph), 134.5 (s, Ph), 137.6 (s, Ph), 170.0 (s, 2C, C_3 and $\underline{C}OOCH_2CH_3$), 172.7 (s, $O\underline{C}OCH_3$). MS *m/z*: M^+ Calcd for $C_{23}H_{23}NO_5$ 393.1575. Found: 393.1583.

ii) Reduction of **2a** (100 mg) gave **15** (69 mg, 61%) and **13** (26 mg, 25%). **15**: (1*S**,4*S**,5*R**,7*S**)-4-Acetoxy-5-ethoxycarbonyl-1,7-diphenyl-2-azabicyclo[3.2.0]heptan-3-one. Colorless prisms from CH_2Cl_2–Et_2O, mp 163—166 °C. IR: 1760, 1715, 1700, 1690. UV: 259 sh (1300). ^{1}H-NMR: 0.82 (3H, t, *J*=7 Hz, $COOCH_2C\underline{H}_3$), 2.19 (3H, s, OAc), 2.62 (1H, dd, *J*=9, 12 Hz, C_6-H), 2.93 (1H, dd, *J*=10, 12 Hz, C_6-H), 3.82 (2H, m, $COOC\underline{H}_2CH_3$), 4.72 (1H, dd, *J*=9, 10 Hz, C_7-H), 6.01 (1H, s, C_4-H), 7.1—7.5 (10H, m, Ar-H). ^{13}C-NMR: 13.6 (q, $COOCH_2\underline{C}H_3$), 20.5 (q, $OCO\underline{C}H_3$), 23.5 (t, C_6), 42.4 (d, C_7), 56.0 (s, C_5), 61.5 (t, $COO\underline{C}H_2CH_3$), 69.0 (s, C_1), 73.4 (d, C_4), 126.6 (d, 2C, Ph), 127.3 (d, Ph), 127.6 (d, 2C, Ph), 128.7 (d, 3C, Ph), 128.8 (d, 2C, Ph), 137.1 (s, Ph), 138.1 (s, pH), 169.3 (s, C_3), 169.3 (s, $\underline{C}OOCH_2CH_3$), 171.7 (s, $O\underline{C}OCH_3$). *Anal.* Calcd for $C_{13}H_{23}NO_5$: C, 70.21; H, 5.89; N, 3.56. MS *m/z*: 393.1574. Found: C, 69.96; H, 5.86; N, 3.50. M^+ *m/z*: 393.1531.

iii) Reduction of **6** (100 mg) gave **16** (57 mg, 51%). **16**: (1*S**,4*R**,5*R**,6*R**,7*R**)-4-Acetoxy-6-deuterio-5-ethoxycarbonyl-1,7-diphenyl-2-azabicyclo[3.2.0]heptan-3-one. Colorless prisms from CH_2Cl_2–Et_2O, mp 215—220 °C. IR: 1750, 1715, 1710. UV: 260 sh (4400). ^{1}H-NMR: 0.76 (3H, t, *J*=7 Hz, $COOCH_2C\underline{H}_3$), 2.13 (3H, s, OAc), 2.87 (1H, d, *J*=9 Hz, C_6-H), 3.71 (2H, q, *J*=7 Hz, $COOC\underline{H}_2CH_3$), 4.14 (1H, d, *J*=9 Hz, C_7-H), 5.97 (1H, s, C_4-H), 6.85—7.25 (10H, m, Ar-H), 7.71 (1H, s, NH). MS *m/z*: M^+ Calcd for $C_{23}H_{22}DNO_5$ 394.1639. Found: 394.1659.

iv) Reduction of **8** (100 mg) gave **17** (69 mg, 61%) and **16** (13 mg, 12%). **17**: (1*S**,4*S**,5*R**,6*S**,7*S**)-4-Acetoxy-6-deuterio-5-ethoxycarbonyl-1,7-diphenyl-2-azabicyclo[3.2.0]heptan-3-one. Colorless prisms from CH_2Cl_2–Et_2O, mp 169—172 °C. IR (CH_2Cl_2): 3380, 1750, 1720. UV: 260 sh (2200). ^{1}H-NMR: 0.82 (3H, t, *J*=7 Hz, $COOCH_2C\underline{H}_3$), 2.19 (3H, s, OAc), 2.92 (1H, d, *J*=9 Hz, C_6-H), 3.82 (2H, m, $COOC\underline{H}_2CH_3$), 4.74 (1H, d, *J*=9 Hz, C_7-H), 5.89 (1H, s, NH), 6.02 (1H, s, C_4-H), 8.02—8.44 (10H, m, Ar-H). MS *m/z*: M^+ Calcd for $C_{23}H_{22}DNO_5$ 394.1639. Found: 394.1651.

v) Reduction of **1f** (100 mg) gave **18** (45 mg, 40%), **19** (40 mg, 36%) and **20** (15 mg, 13%). **18**: (1*S**,4*R**,5*R**,7*R**)-4-Acetoxy-5-ethoxycarbonyl-7-methyl-1,7-diphenyl-2-azabicyclo[3.2.0]heptan-3-one. Colorless amorphous solid. IR (CH_2Cl_2): 1745, 1715, 1700. UV: 260 sh (300). ^{1}H-NMR: 0.62 (3H, t, *J*=7 Hz, $COOCH_2C\underline{H}_3$), 1.48 (3H, s, CH_3), 2.10 (3H, s, OAc), 2.59 (1H, d, *J*=13, C_6-H), 3.58 (2H, m, $COOC\underline{H}_2CH_3$), 3.70 (1H, d, *J*=13 Hz, C_6-H), 5.94 (1H, s, C_4-H), 6.65—7.5 (10H, m, Ar-H), 9.11 (1H, s, NH). ^{13}C-NMR: 13.3 (q, $COOCH_2\underline{C}H_3$), 20.4 (q, $OCO\underline{C}H_3$), 29.6 ($\underline{C}H_3$), 38.5 (t, C_6), 51.7 (s, C_7), 55.0 (s, C_5), 60.6 (t, $COO\underline{C}H_2CH_3$), 73.3 (s, C_1), 77.3 (d, C_4), 125.5 (d, Ph), 125.7 (d, 2C, Ph), 126.5 (d, 2C, Ph), 126.7 (d, Ph), 127.3 (d, 2C, Ph), 127.8 (d, 2C, Ph), 137.9 (s, Ph), 146.0 (s, Ph), 168.6 (s, C_3), 169.7 (s, $\underline{C}OOCH_2CH_3$), 174.5 (s, $O\underline{C}OCH_3$). **19**: (1*S**,4*S**,5*R**,7*R**)-4-Acetoxy-5-ethoxycarbonyl-7-methyl-1,7-diphenyl-2-azabicyclo-[3.2.0]heptan-3-one. Colorless amorphous solid. IR (CH_2Cl_2): 1740, 1720, 1710. UV: 260 sh (500). ^{1}H-NMR: 0.70 (3H, t, *J*=7 Hz, $COOCH_2$-$C\underline{H}_3$), 1.52 (3H, s, CH_3), 2.19 (1H, d, *J*=13 Hz, C_6-H), 2.26 (3H, s, OAc), 3.66 (1H, d, *J*=13 Hz, C_6-H), 3.71 (2H, m, $COOC\underline{H}_2CH_3$), 5.76 (1H, s, C_4-H), 6.8—7.4 (10H, m, Ar-H), 9.45 (1H, s, NH). ^{13}C-NMR: 13.4 (q, $COOCH_2\underline{C}H_3$), 20.3 (q, $OCO\underline{C}H_3$), 29.9 (t, C_6), 30.3 (q, $\underline{C}H_3$), 51.7 (s, C_7), 53.6 (s, C_5), 61.4 (t, $COO\underline{C}H_2CH_3$), 73.0 (s, C_7), 75.0 (d, C_4), 125.6 (d, Ph), 126.6 (d, 3C, Ph), 127.1 (d, 3C, Ph), 127.8 (d, 2C, Ph), 128.2 (d, Ph), 136.1 (s, Ph), 145.3 (s, Ph), 169.9 (s, C_3), 170.7 (s, $\underline{C}OOCH_2CH_3$), 174.1 (s, $O\underline{C}OCH_3$). **20**: (1*S**,4*S**,5*R**,7*S**)-4-Acetoxy-5-ethoxycarbonyl-7-methyl-1,7-diphenyl-2-azabicyclo[3.2.0]heptan-3-one. Colorless prisms from CH_2Cl_2–Et_2O, mp 71—74 °C and 139—140 °C. IR: 1750, 1720 sh, 1710. UV: 260 sh (500). ^{1}H-NMR: 1.09 (3H, t, *J*=7 Hz, $COOCH_2C\underline{H}_3$), 1.64 (3H, s, CH_3), 2.18 (3H, s, OAc), 2.18 (1H, d, *J*=13 Hz, C_6-H), 2.99 (1H, d, *J*=13 Hz, C_6-H), 4.17 (2H, m, $COOC\underline{H}_2CH_3$), 5.92 (1H, s, C_4-H), 6.34 (1H, br s, NH), 6.9—7.4 (10H, m, Ar-H). ^{13}C-NMR: 13.7 (q, $COOCH_2\underline{C}H_3$), 20.5 (q, $OCO\underline{C}H_3$), 28.5 (q, CH_3), 30.5 (t, C_6), 50.9 (s, C_7), 54.4 (s, C_5), 61.9 (t, $COO\underline{C}H_2CH_3$), 70.3 (s, C_1), 75.1 (d, C_4), 125.2 (d, 2C, Ph), 126.5 (d, Ph), 127.1 (d, 2C, Ph), 128.0 (d, 2C, Ph), 128.2 (d, Ph), 129.0 (d, 2C, Ph), 136.6 (s, Ph), 145.1 (s, Ph), 169.4 (s, C_3), 169.8 (s, $\underline{C}OOCH_2CH_3$), 171.1 (s, $O\underline{C}OCH_3$). *Anal.* Calcd for $C_{24}H_{25}NO_5$: C, 70.74; H, 6.18; N, 3.41. Found: C, 70.70; H, 6.15; N, 3.38.

vi) Reduction of **2f** (100 mg) gave **20** (56 mg, 50%).

vii) Reduction of **2b** (100 mg) gave (1*S**,4*S**,5*R**,7*R**)-4-acetoxy-7-ethoxy-5-ethoxycarbonyl-1-phenyl-2-azabicyclo[3.2.0]heptan-3-one **21** (73 mg, 64%) as colorless prisms from CH_2Cl_2–Et_2O, mp 158—160 °C. IR: 3300, 1740, 1720, 1700. UV: 262 sh (2000). ^{1}H-NMR: 0.86 (3H, t, *J*=7 Hz, $COOCH_2C\underline{H}_3$), 1.17 (3H, t, *J*=7 Hz, $OCH_2C\underline{H}_3$), 2.13 (3H, s, OAc), 2.29 (1H, dd, *J*=8, 13 Hz, C_6-H), 2.88 (1H, dd, *J*=8, 13 Hz, C_6-H), 3.47 (2H, q, *J*=7 Hz, $OC\underline{H}_2CH_3$), 3.79 (2H, qd, *J*=7, 4 Hz, $COOC\underline{H}_2CH_3$), 4.81 (1H, t, *J*=8 Hz, C_7-H), 6.03 (1H, s, C_4-H), 6.84 (1H, s, NH), 7.35 (5H, br s, Ar-H). ^{13}C-NMR: 13.5 (q, $COOCH_2\underline{C}H_3$), 15.1 (q, $OCH_2\underline{C}H_3$), 20.5 (q, $OCO\underline{C}H_3$), 28.2 (t, C_6), 52.4 (s, C_5), 61.5 (t, $COO\underline{C}H_2CH_3$), 64.8 (t, $O\underline{C}H_2CH_3$), 69.2 (s, C_1), 72.3 (d, C_7), 73.4 (d, C_4), 126.0 (d, 2C, Ph), 128.6 (d, 3C, Ph), 137.4 (s, Ph), 169.4 (s, C_3), 169.7 (s, $\underline{C}OOCH_2CH_3$), 171.8 (s, $O\underline{C}OCH_3$). *Anal.* Calcd for $C_{19}H_{23}NO_6$: C, 63.14; H, 6.42; N, 3.88. MS *m/z*: 361.1524. Found: C, 63.10; H, 6.49; N, 3.83. M^+ *m/z*: 361.1499.

viii) Reduction of **1e** (100 mg) gave (1*S**,4*S**,5*R**,7*R**)-4,7-diacetoxy-5-ethoxycarbonyl-7-methyl-1-phenyl-2-azabicyclo[3.2.0]heptan-3-one **22** (68 mg, 66%). Colorless prisms, mp 168—170 °C. IR: 1760, 1750, 1735, 1715. UV: 258 sh (200). ^{1}H-NMR: 1.10 (3H, t, *J*=7 Hz, $COOCH_2C\underline{H}_3$), 1.69 (3H, s, CH_3), 2.00 (3H, s, OAc), 2.15 (3H, s, OAc), 2.77 (1H, d, *J*=12 Hz, C_6-H), 2.98 (1H, d, *J*=12 Hz, C_6-H), 4.12 (2H, m, $COOC\underline{H}_2CH_3$), 6.09 (1H, s, C_4-H), 7.09 (1H, s, NH), 7.24—7.4 (5H, m, Ar-H). ^{13}C-NMR: 13.7 (q, $COOCH_2\underline{C}H_3$), 20.4 (q, $OCO\underline{C}H_3$), 21.4 (q, $OCO\underline{C}H_3$), 22.2 (q, $\underline{C}H_3$), 35.8 (t, C_6), 52.4 (s, C_5), 62.1 (t, $COO\underline{C}H_2CH_3$), 71.2 (s, C_1), 73.9 (d, C_4), 81.6 (s, C_7), 126.5 (d, 2C, Ph), 128.3 (d, 2C, Ph), 135.8 (s, Ph), 169.4 (s, C_3), 169.8 (s, $\underline{C}OOCH_2CH_3$), 170.1 (s, $O\underline{C}OCH_3$), 170.3 (s, $OCOCH_3$). MS *m/z*: M^+ Calcd for $C_{20}H_{23}NO_7$ 389.1475. Found: 389.1487.

ix) Reduction of **1d** (325 mg) gave (1*S**,4*R**,5*R**,7*S**)-4-acetoxy-5-ethoxycarbonyl-7-ethyl-1-phenyl-2-azabicyclo[3.2.0]heptan-3-one **23** (220 mg, 59%). Colorless prisms, mp 204—207 °C. IR: 3150, 3050, 1760, 1710. ^{1}H-NMR: 0.67 (3H, t, *J*=7 Hz, $CH_2C\underline{H}_3$), 0.79 (3H, t, *J*=7 Hz, $COOCH_2C\underline{H}_3$), 1.16—2.35 (2H, m, $C\underline{H}_2CH_3$), 2.11 (3H, s, OAc), 2.4—2.6 (3H, m, C_6-H and C_7-H), 3.83 (2H, q, *J*=7 Hz, $COOC\underline{H}_2CH_3$), 5.84 (1H, s, C_4-H), 7.2—7.4 (5H, m, Ar-H), 8.30 (1H, br s, NH). ^{13}C-NMR: 11.1 (q, $CH_2\underline{C}H_3$), 13.5 (q, $COOCH_2\underline{C}H_3$), 20.5 (q, $OCO\underline{C}H_3$), 23.2 (t, $\underline{C}H_2CH_3$), 31.6 (t, C_6), 49.9 (d, C_7), 55.9 (s, C_1), 60.5 (t, $COO\underline{C}H_2CH_3$), 69.9 (s, C_1), 77.9 (d, C_4), 124.6 (d, 2C, Ph), 127.3 (d, Ph), 128.5 (d, 2C, Ph), 136.2 (s, Ph), 168.9 (s, C_3), 169.7 (s, $\underline{C}OOCH_2CH_3$), 173.4 (s, $O\underline{C}OCH_3$). *Anal.* Calcd for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.06. Found: C, 65.84; H, 6.80; N, 3.89.

Catalytic Hydrogenation of 24 A solution of **24**[15] (380 mg) in AcOH (20 ml) was hydrogenated over PtO_2 (40 mg) at room temperature for 4 h. After removal of the catalyst, the filtrate was concentrated to dryness. Crystallization of the residue from Et_2O gave the alcohol (300 mg, 67%) as colorless prisms, mp 250—255 °C. The alcohol (250 mg) was treated with Ac_2O (1 ml) and pyridine (2 ml) at room temperature overnight. Crystallization of the product from CH_2Cl_2–Et_2O gave **13** (225 mg, 80%).

Alkylation of 1a with Triethyloxonium Fluoroborate A solution of **1a** (200 mg) in CH_2Cl_2 (10 ml) was treated with excess $Et_3O^+BF_4^-$ at room temperature overnight. The reaction mixture was diluted with CH_2Cl_2, and washed with 5% $NaHCO_3$ and water. The organic layer was dried over Na_2SO_4 and evaporated *in vacuo*. The residue in benzene was passed through a short column of SiO_2. Crystallization of the eluate from Et_2O–hexane gave (1*S**,5*R**,7*R**)-3-ethoxy-5-ethoxycarbonyl-1,7-diphenyl-2-azabicyclo[3.2.0]hept-2-en-4-one **25** (173 mg, 80%) as colorless prisms, mp 133—136 °C. IR: 1760, 1740, 1640. UV (dioxane): 260 sh (2000). ^{1}H-NMR: 0.67 (3H, t, *J*=7 Hz, $COOCH_2C\underline{H}_3$), 1.20 (3H, t, *J*=7 Hz, $OCH_2C\underline{H}_3$), 2.38 (1H, dd, *J*=4, 6 Hz, C_6-H), 3.58 (1H, d, *J*=4, 6 Hz, C_6-H), 3.60 (2H, q, *J*=7 Hz, $COOC\underline{H}_2CH_3$), 3.78 (1H, t, *J*=6 Hz, C_7-H), 4.65 (2H, q, *J*=7 Hz, $OC\underline{H}_2CH_3$), 7.1 (10H, br s, Ar-H). *Anal.* Calcd for $C_{23}H_{23}NO_4$: C, 73.19; H, 6.14; N, 3.71. Found: C, 73.43; H, 6.14; N, 3.77.

Photolysis of 25 A solution of **25** (100 mg) in dimethoxyethane (30 ml) was irradiated at 0 °C for 10 h. After evaporation of the solvent *in vacuo*, the residue was chromatographed over SiO_2 in benzene to give (1*S**,5*R**,7*S**)-3-ethoxy-5-ethoxycarbonyl-1,7-diphenyl-2-azabicyclo-[3.2.0]hept-2-en-4-one **26** (50 mg, 50%). Colorless prisms from Et_2O–hexane, mp 122—127 °C. IR: 1745, 1725, 1670, 1620. ^{1}H-NMR: 0.73 (3H, t, *J*=7 Hz, $COOCH_2C\underline{H}_3$), 1.25 (3H, t, *J*=7 Hz, $OCH_2C\underline{H}_3$), 2.27 (1H, dd, *J*=8, 13 Hz, C_6-H), 3.47 (1H, dd, *J*=8, 13 Hz, C_6-H), 3.78 (2H, q, *J*=7 Hz, $COOC\underline{H}_2CH_3$), 4.27 (2H, q, *J*=7 Hz, $OC\underline{H}_2CH_3$), 4.78 (1H, t, *J*=8 Hz, C_7-H), 7.2 (10H, m, Ar-H). *Anal.* Calcd for $C_{23}H_{23}NO_4$: C, 73.16; H, 6.14; N, 3.71. Found: C, 73.15; H, 6.11; N, 3.63.

Alkylation of 2a with Triethyloxonium Fluoroborate **2a** (200 mg) was similarly alkylated with excess $Et_3O^+BF_4^-$ to give **26** (140 mg, 65%). This was identical with the imidate **26** obtained by photolysis of **25**.

Alkylation of 6 with Triethyloxonium Fluoroborate **6** (107 mg) was similarly alkylated with excess $Et_3O^+BF_4^-$ to give (1*S**,5*R**,6*R**,7*R**)-6-deuterio-3-ethoxy-4-ethoxycarbonyl-1,7-diphenyl-2-azabicyclo[3.2.0]hept-2-en-4-one **27** (110 mg, 95%). Colorless prisms from Et_2O–hexane, mp 126—128 °C. IR: 1740, 1720, 1638, 1600. ^{1}H-NMR: 0.61 (3H, t, *J*=7 Hz, $COOCH_2C\underline{H}_3$), 1.56 (3H, t, *J*=7 Hz, $OCH_2C\underline{H}_3$), 2.38 (1H, d, *J*=10 Hz, C_6-H), 3.62 (1H, d, *J*=10 Hz, C_7-H), 3.72 (2H, q, *J*=7 Hz, $COOC\underline{H}_2CH_3$),

4.66 (2H, q, $J=7$ Hz, $OC\underline{H}_2CH_3$), 7.07 (10H, br s, Ar-H). MS m/z: M^+ Calcd for $C_{23}H_{22}DNO_4$ 378.1690. Found: 378.1722.

Photolysis of 27 A solution of **27** (70 mg) in dimethoxyethane (20 ml) was similarly irradiated to give (1*S**,5*R**,6*S**,7*S**)-6-deuterio-3-ethoxy-4-ethoxycarbonyl-1,7-diphenyl-2-azabicyclo[3.2.0]hept-2-en-4-one **28** (18 mg, 26%). Colorless prisms from Et_2O–hexane, mp 130—132 °C. IR: 1750, 1730, 1620. ^{1}H-NMR: 0.64 (3H, t, $J=7$ Hz, $COOCH_2C\underline{H}_3$), 1.26 (3H, t, $J=7$ Hz, $OCH_2C\underline{H}_3$), 3.43 (1H, d, $J=10$ Hz, C_6-H), 3.79 (2H, q, $J=7$ Hz, $COOC\underline{H}_2CH_3$), 4.27 (2H, m, $OC\underline{H}_2CH_3$), 4.78 (1H, d, $J=10$ Hz, C_7-H), 6.9—7.5 (10H, m, Ar-H). MS m/z: M^+ Calcd for $C_{23}H_{22}DNO_4$ 378.1690. Found: 378.1755.

Alkylation of 8 with Triethyloxonium Fluoroborate **8** (50 mg) was similarly alkylated with excess $Et_3O^+BF_4^-$ to give **28** (47 mg, 87%). This was identical with the imidiate **28** obtained by photolysis of **27**.

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References and Notes

1) Part XLI: T. Sano, Y. Horiguchi, H. Takayanagi, H. Ogura, and Y. Tsuda, *Chem. Pharm. Bull.*, **36**, 3130 (1988).
2) T. Sano, Y. Horiguchi, and Y. Tsuda, *Heterocycles*, **16**, 355 (1981).
3) T. Sano, Y. Horiguchi, Y. Tsuda, K. Furuhata, H. Takayanagi, and H. Ogura, *Chem. Pharm. Bull.*, **35**, 9 (1987).
4) T. Sano, Y. Horiguchi, and Y. Tsuda, *Heterocycles*, **12**, 1427 (1979).
5) T. Sano, Y. Horiguchi, and Y. Tsuda, *Chem. Pharm. Bull.*, **35**, 23 (1987).
6) To simplify descriptions, we adopt the following abbreviations hereafter: α = *endo*, β = *exo*, D = deuterium, Ph = phenyl, Me = methyl, Et = ethyl, and OAc = acetoxyl.
7) If the starting material is chiral, the product should be the enantiomer **8*** of the 7α-Ph derivative **8**.
8) C. M. Metzler, "NONLIN, A Computer Program for Parameter Estimation in Nonlinear Situations" Technical Report. 729/69/7297/005, Upjohn Co., Kalamazoo, Mich.
9) A. P. Marchand, "Stereochemical Applications of NMR Studies in Rigid Bicyclic System," Verglag Chemie International Inc., Florida, 1982, p. 59.
10) T. Sano, Y. Horiguchi, S. Kambe, J. Toda, J. Taga, and Y. Tsuda, *Heterocycles*, **16**, 893 (1981).
11) T. Sano, Y. Horiguchi, and Y. Tsuda, *Heterocycles*, **16**, 889 (1981).
12) The X-ray analyses showed that both the C_1–C_5 and C_1–C_7 bonds in the cyclobutane are unusually elongated compared to the other single bonds (see ref. 3).
13) T. Sano, J. Toda, and Y. Tsuda, *Heterocycles*, **22**, 53 (1984).
14) T. Sano, J. Toda, Y. Tsuda, K. Yamaguchi, and S. Sakai, *Chem. Pharm. Bull.*, **32**, 3255 (1984).
15) T. Sano, Y. Horiguchi, and Y. Tsuda, *Heterocycles* **9**, 731 (1978).