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Studies on 2,5-Diaryl-2,4-dihydro-3*H*-pyrazol-3-ones. II.[1] Synthesis of 4-Cycloalkyl-2,5-diaryl-2,4-dihydro-3*H*-pyrazol-3-ones Using the Tautomeric Properties of 2,5-Diaryl-2,4-dihydro-3*H*-pyrazol-3-ones

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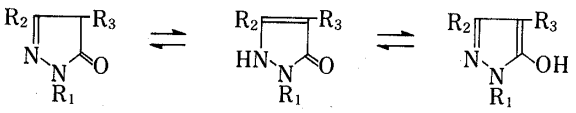
The reaction of 2-aryl-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-ones (**1**) with cyclopentanone (**5a**) in the absence of NEt_3 gives 2-aryl-4-cyclopentylidene-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-ones (**7**) in nearly quantitative yield. In the presence of NEt_3, the reaction of **1** with **5a** gives 2-aryl-4-cyclopentyl-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-ones (**6a—c**) in *ca.* 40% yields together with epoxides (**8a—c**). Similarly, various 4-cycloalkyl-2-aryl-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-ones (**6d—i**) were obtained in *ca.* 40% yields. In these reactions, the expected cycloalkylidene products were reduced to cycloalkyl derivatives. The reaction mechanisms and the synthetic utility of these reactions are discussed.

Keywords——tautomerism; 2,4-dihydro-3*H*-pyrazol-3-one; cycloalkylation; oxidation–reduction reaction; ionic reaction; base-catalyzed reaction; hydride migration

Introduction

The introduction of an alkyl substituent at the desired position of heterocycles is important because heterocycles are often key intermediates in the synthesis of pharmaceutical drugs. We have been interested in the 2,4-dihydro-3*H*-pyrazol-3-one skeleton because this is the mother skeleton of pyrine drugs which show analgesic or anti-inflammatory activities. This skeleton exists in three tautomeric forms as shown in Chart 1. In polar solvents, a 2,4-dihydro-3*H*-pyrazol-3-one such as **1** exists predominantly in its OH (C) or NH form (B), while in non-polar solvents it exists mainly in its CH form (A).[2]



A CH form ⇌ B NH form ⇌ C OH form

Chart 1

In the course of our attempts to utilize this characteristic property of 2,4-dihydro-3*H*-pyrazol-3-ones (**1**) in organic synthesis, we found a general procedure for the conversion of **1** to highly substituted 1*H*-indazoles (**4**).[1] In this transformation, the key step is the tautomerism of **2** to **2′** catalyzed by a tertiary amine (NEt_3).

With the aim of extending the above conversions, we examined the reaction of **1** with cycloalkanones (**5a—c**) in the presence of triethylamine (NEt_3), but the reaction mode was completely changed. Thus, 4-cycloalkyl-2,4-dihydro-3*H*-pyrazol-3-ones were obtained in *ca.* 40% yields. In this report, we deal with the mechanism of these curious reactions.

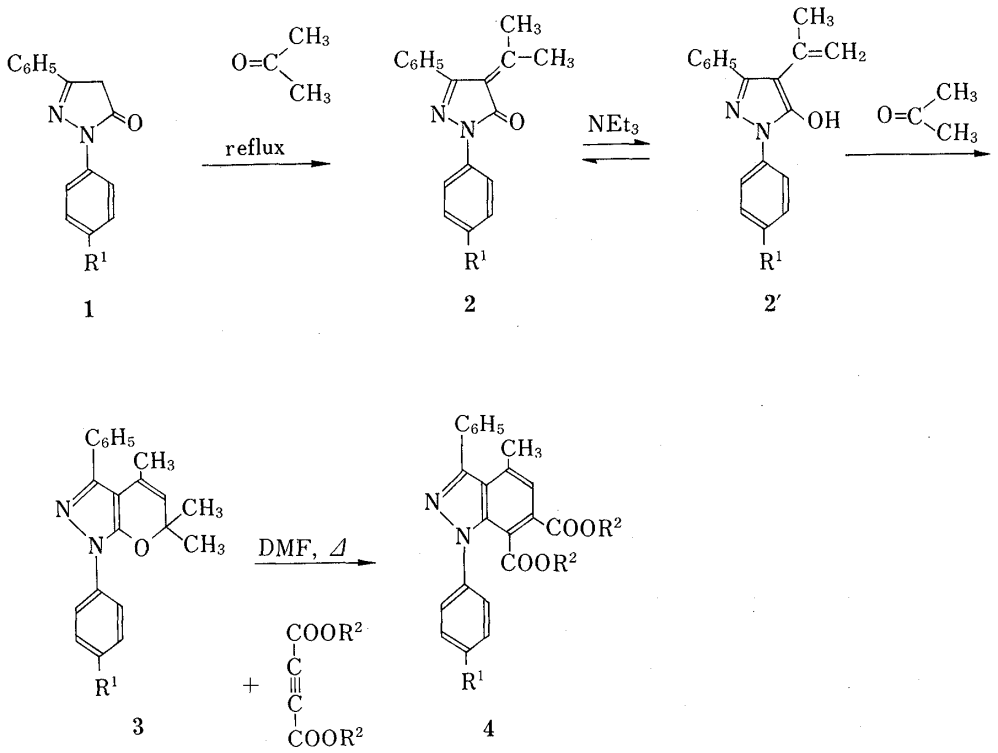


Chart 2

Results

It is fairly well known that active methylene at the 4-position of 2,4-dihydro-3*H*-pyrazol-3-ones (**1**) reacts smoothly with ketones to produce the corresponding 4-alkylidene-2,4-dihydro-3*H*-pyrazol-3-ones (**2**) in nearly quantitative yields.[1,3] These reactions also occur with cycloalkanones.

From the reaction of **1** with cyclopentanone (**5a**) in the absence of NEt_3 at reflux, we obtained 2-aryl-4-cyclopentylidene-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-ones (**7a—c**) in high yields (Table I). The structures of **7** were determined on the basis of spectroscopic data and elemental analyses. For example, in the case of **7a** the molecular formula was confirmed to be $C_{20}H_{18}N_2O$ by mass spectroscopy (M^+, 302) and elemental analysis (the physical properties of **7** are summarized in Tables VI and IX).

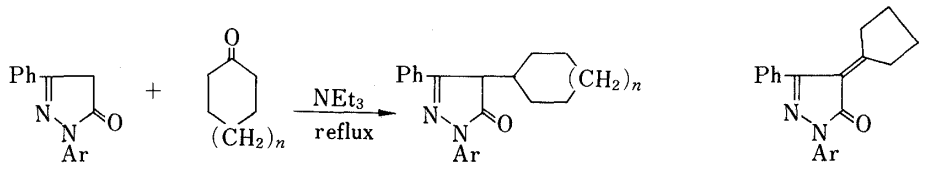
In the presence of NEt_3, the reaction of **1** with **5a** was completely altered. From the reaction of **1a** with **5a** at reflux for 12 h in the presence of 10 mol eq of NEt_3, we obtained 4-cyclopentyl-2,5-diphenyl-2,4-dihydro-3*H*-pyrazol-3-one (**6a**) in 42% yield. The structure of **6a** was determined on the basis of elemental analysis and spectroscopic data. The molecular formula was confirmed to be $C_{20}H_{20}N_2O$ by elemental analysis and mass spectroscopy (M^+, 304). The proton nuclear magnetic resonance (^{1}H-NMR) spectrum revealed a multiplet at 1.19—2.20 ppm (9H) due to a cyclopentyl substituent at the 4-position of the ring, a doublet at 3.71 ppm due to a methine proton of the ring, and an aromatic multiplet at 7.16—8.10 ppm (10H). The signals corresponding to the methylene protons of **1** had completely disappeared. In addition, no signals corresponding to **7a** were observed in the ^{1}H-NMR spectrum of the gross reaction mixture of **1a** and **5a**. The carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectrum revealed three triplets at 28.24, 27.83, and 24.98 (2C) ppm due to the four methylene carbons of the cyclopentyl group, and two doublets at 41.00 and 51.52 ppm due to the cyclopentyl carbon attached to the ring and the 4-position carbon of the ring. No signals corresponding to **1a** or **7a** were observed. The infrared (IR) spectrum showed absorption

TABLE I. 2-Aryl-4-cyclopentylidene-2,4-dihydro-3*H*-pyrazol-3-ones (**7**)

Compd. No.	Ar	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd (Found)				
					C	H	Br	Cl	N
7a	Phenyl	128—130	90	$C_{20}H_{18}N_2O$	79.44 (79.42)	6.00 (5.95)			9.26 (9.19)
7b	4-Br-Ph	172—173	88	$C_{20}H_{17}BrN_2O$	63.01 (62.83)	4.49 (4.27)	30.96 (20.90)		7.35 (7.44)
7c	4-Cl-Ph	167—169	88	$C_{20}H_{17}ClN_2O$	71.32 (71.29)	5.09 (5.11)		10.53 (10.62)	8.32 (8.34)

TABLE II. 2-Aryl-4-cycloalkyl-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-ones (**6**)

Compd. No.	Ar	R	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd (Found)				
						C	H	Br	Cl	N
6a	Phenyl	Cyclopentyl	153—154	42	$C_{20}H_{20}N_2O$	78.83 (78.92)	6.57 (6.62)			9.04 (9.20)
6b	4-Br-Ph	Cyclopentyl	184—185	42	$C_{20}H_{19}BrN_2O$	62.53 (62.70)	5.04 (4.96)	21.75 (21.82)		7.08 (7.31)
6c	4-Cl-Ph	Cyclopentyl	166—167	40	$C_{20}H_{19}ClN_2O$	70.56 (70.82)	5.41 (5.61)		10.60 (10.48)	8.23 (8.26)
6d	Phenyl	Cyclohexyl	142—144	43	$C_{21}H_{22}N_2O$	79.42 (79.21)	7.16 (6.96)			8.98 (8.80)
6e	4-Br-Ph	Cyclohexyl	188—189	40	$C_{21}H_{21}BrN_2O$	63.47 (63.51)	5.24 (5.29)	19.83 (20.12)		7.03 (7.05)
6f	4-Cl-Ph	Cyclohexyl	184—185	38	$C_{21}H_{21}ClN_2O$	71.54 (71.48)	5.98 (6.00)		10.13 (10.05)	8.01 (7.94)
6g	Phenyl	Cycloheptyl	133—134	40	$C_{22}H_{24}N_2O$	79.43 (79.48)	7.26 (7.28)			8.39 (8.43)
6h	4-Br-Ph	Cycloheptyl	170—171	35	$C_{22}H_{23}BrN_2O$	63.93 (64.27)	5.54 (5.59)	18.95 (19.44)		6.69 (6.89)
6i	4-Cl-Ph	Cycloheptyl	174—175	37	$C_{22}H_{23}ClN_2O$	72.02 (72.06)	6.29 (6.27)		9.57 (9.67)	7.62 (7.64)



1a—c **5a—c** **6a—i** **7a—c**

1a : Ar=C_6H_5 **5a** : n=0 **6a—c** : n=0 **7a** : Ar=C_6H_5

1b : Ar=4-Br-C_6H_4 **5b** : n=1 **6d—f** : n=1 **7b** : Ar=4-Br-C_6H_4

1c : Ar=4-Cl-C_6H_4 **5c** : n=2 **6g—i** : n=2 **7c** : Ar=4-Cl-C_6H_4

Chart 3

bands similar to those of **1a**. The strong carbonyl absorption band which was observed in the case of **7a** was absent (the physical properties of **6** are summarized in Tables VII and X). Similarly, from the reactions of **1a—c** with **5a—c** in the presence of NEt_3 at reflux, we obtained various 2,5-diaryl-4-cycloalkyl-2,4-dihydro-3*H*-pyrazol-3-ones (Table II).

Discussion

By means of these reactions, various cycloalkylidene moieties were easily reduced to cycloalkyl substituents at the 4-position of 2,5-diaryl-2,4-dihydro-3*H*-pyrazol-3-one rings. We wished to elucidate the reaction mechanism not only in order to extend the above conversions to other heterocycles or alkanones, but also to apply these systems as reducing catalysts.

In order to establish the reaction mechanism, the following points should be clarified: (i) the nature of the oxidized product during the reaction; (ii) the effect of base; (iii) the effect of temperature; (iv) the H source for the cycloalkyl substituent; (v) the reaction mode (ionic or radical reaction). Using **1a** and **5a** (or **7b** and **5a**), we examined the reaction course in detail.

(i) Oxidized Product during the Reaction

Since the reduction product **6** was obtained, some other species must be oxidized during the reaction course. We isolated the epoxide **8a** (38%) and **6a** (40%) from the reaction mixture by alumina (neutral) column chromatography using benzene as an eluent. The molecular formula of the epoxide **8a** was confirmed by mass spectroscopy (M^+, 318) and elemental analysis. The ^{1}H-NMR spectrum revealed a multiplet at 1.88—2.20 ppm due to the cyclopentyl substituent at the 4-position of the ring (8H) and an aromatic multiplet at 7.17—8.10 ppm (10H). The ^{13}C-NMR spectrum revealed two characteristic carbons at 80.33 and 66.23 ppm (both singlets) due to the carbons of the epoxide ring. The IR spectrum showed a strong carbonyl absorption band at 1715 cm^{-1} and a C–O stretching absorption band in the 1260 cm^{-1} region (the physical properties of **8a**—**c** are summarized in Tables VIII and XI). The epoxides **8b**, **c** were similarly obtained, while no epoxides could be obtained from the reaction of **1a**—**c** with **5b**, **c**. In these cases, we obtained $\overset{+}{N}Et_3$–O^- as an oxidized product. It is possible that under the reaction conditions used, epoxides adjacent to 6- or 7-membered rings might be deoxygenated. In support of this, the epoxide **8a** was also deoxygenated when it was refluxed in benzene solution in the presence of NEt_3 or PPh_3. When the reaction of **1a** or **1b** with **5a** was carried out for a long time under reflux, triethylamine oxide ($\overset{+}{N}Et_3$–O^-) was also obtained from the reaction.

TABLE III. 2-Aryl-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-one-4-cyclopentylidene-epoxides (**8**)

Compd. No.	Ar	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd (Found)				
					C	H	Br	Cl	N
8a	Phenyl	152—154	35	$C_{20}H_{18}N_2O_2$	75.45 (75.19)	5.70 (5.63)			8.80 (8.65)
8b	4-Br–Ph	164—165	40	$C_{20}H_{17}BrN_2O_2$	60.47 (60.22)	4.31 (4.06)	20.11 (19.95)		7.05 (7.21)
8c	4-Cl–Ph	150—152	42	$C_{20}H_{17}ClN_2O_2$	68.09 (68.23)	4.86 (4.59)		10.05 (9.78)	7.94 (8.10)

(ii) Effect of Base

In the absence of NEt_3, the reaction of **1a** with **5a** gave exclusively **7a** and **6a** could not be detected at all in the reaction medium. Thus, the added bases (NEt_3) might affect the electronic state of **1**. If so, the changes of **1** upon the addition of NEt_3 might be detectable spectroscopically. We measured the ^{1}H-NMR spectrum of **1a** in CD_3COCD_3 in the absence and presence of NEt_3. In the absence of NEt_3, **1a** is present as a mixture of OH (C) and CH (A) forms (OH 75%, CH 25%).[4] Assignments of signals were as follows: the signal observed at 8.00 ppm (d, 2H, J=8.1 Hz) was due to *ortho* protons of the *N*-phenyl substituent (OH

form), that at 7.99 ppm (d, 2H, $J=7.6$ Hz) was due to *ortho* protons of the *N*-phenyl substituent (CH form) that at 7.84 ppm (dd, 2H, $J=1.5$, 7.3 Hz) was due to *ortho* protons of the 5-phenyl substituent (OH and CH forms), that at 7.46—7.34 ppm (m, 5H) was due to *meta* protons of the *N*- and 5-phenyl substituent and the *para* proton of the 5-phenyl substituent (OH and CH forms), that at 7.23 ppm (d, 1H, $J=7.6$ Hz) was due to the *para* proton of the *N*-phenyl substituent (CH form), that at 7.20 ppm (t like, 1H, $J=7.3$ Hz) was due to the *para* proton of the *N*-phenyl substituent (OH form), that at 6.01 ppm (s, 1H) was due to the 4-H proton of the OH form and that at 3.98 ppm (2H) was due to methylene protons at the 4-position of the CH form (the signal observed at 3.98 ppm (2H) is large, but H_2O present in the solvent is also included in this peak). In the presence of NEt_3, the ^{1}H-NMR spectrum of **1a** was completely changed and simplified. Assignments of signals were as follows: the signal observed at 8.12 ppm (dd, 2H, $J=1.5$, 7.3 Hz) was due to *ortho* protons of the *N*-phenyl substituent, that at 7.82 ppm (dd, 2H, $J=1.6$, 8.3 Hz) was due to *ortho* protons of the 5-phenyl substituent, that at 7.40—7.29 ppm (m, 5H) was due to *meta* protons of the *N*- and 5-phenyl substituents and 4-H proton in the ring, and that at 7.22 ppm (t like, 1H, $J=7.3$ Hz) was due to the *para* proton of the *N*-phenyl substituent. Clearly, the signals were simplified and the signals observed at 6.01 ppm (C_4-H proton of OH form) and 3.98 ppm (CH_2 protons of CH form) had completely disappeared. Further, the *ortho* protons of the *N*-phenyl substituent are shifted slightly to lower field (0.11 ppm), which suggests the presence of a cation such as $\overset{+}{N}HEt_3$. The stable anionic state of **1a** is thought to be either the N^- or O^- form. If so, the cation ($\overset{+}{N}HEt_3$) may be present near these anions, namely the *ortho* protons would be strongly affected by this cation (protons were shifted to lower field), while the other aromatic protons would not. These results clearly show the changes of **1a** induced by the addition of NEt_3.

(iii) Effect of Temperature and H Source

Next, we examined the effect of temperature on the reaction. In the absence of NEt_3 the reaction of **1a** with **5a** at room temperature did not afford any products, while in the presence of NEt_3 it gave the epoxide (43%) and the other oxidized product (23%). In this reaction, however, no **6a** could be dected at all.

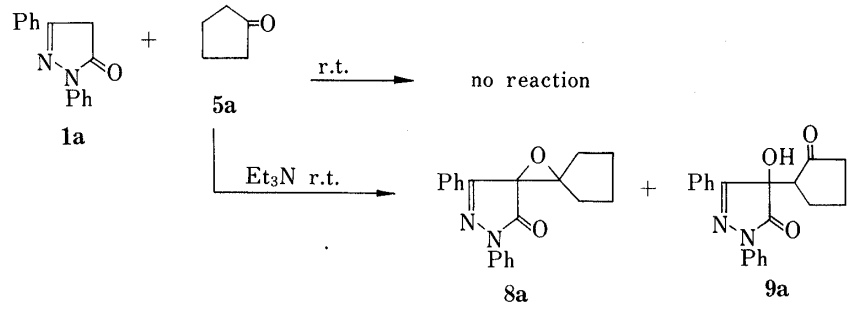


Chart 4

A plausible reaction mechanism for the formation of **9a** is depicted in Chart 5. Thus, 2,5-diphenyl-2,4-dihydro-3*H*-pyrazol-3-one (**1a**) was converted to its delocalized anion state (**1a'**) by NEt_3 catalysis, and then reacted with molecular oxygen to afford the hydroperoxide **10**. The hydroperoxide **10** was smoothly dehydrated to afford the diketone **11**, which was attacked by the enolized cyclopentanone (**5a'**) (in this reaction, we also obtained aliphatic polymeric products derived from cyclopentanone).

In this reaction, the important point is that **6a** could not be detected in the reaction medium; reflux temperature is necessary for the conversion of **1a** to **6a** and **8a**. The difference between reflux temperature and room temperature is the existence (or not) of **7a** in the

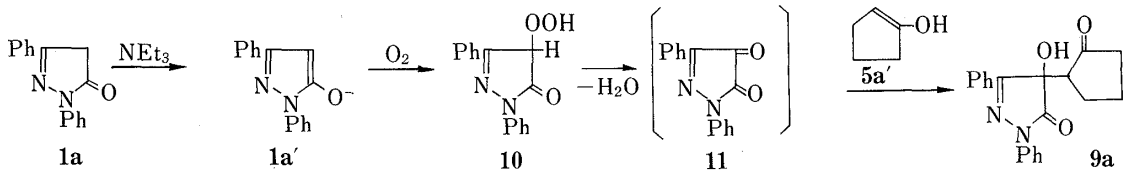


Chart 5

reaction medium. It may be reasonable to consider that **7** is involved as the key intermediate; however, from the reaction of **7a** with **5a** in the presence of NEt_3 we obtained **6a** in less than 10% yield. This low yield of **6a** may be attributable to the absence of water, which is produced under the usual reaction conditions. If so, by using labeled water, one should obtain labeled **6a** (D_2O) and **8a** (H_2O^{18}). Reaction of **7b**[5] (10 mmol) with **5a** in the presence of NEt_3 (100 mmol) and D_2O (1 ml) at reflux was examined. In this run, we obtained **6b** (35%) and **8b** (30%), and we examined the D contents in **6b** (Table IV). From the mass spectroscopic intensities (listed in Table IV), we could calculate the D contents in **6b**, since, 382 (M^+) is the value of the non-labeled Br^{79} compound, 383 is mono-labeled Br^{79}, 384 is di-D-labeled Br^{79} and non-labeled Br^{81}, 385 is mono-labeled Br^{81} and 386 is di-D-labeled Br^{81}. The standard sample mass spectroscopic intensities were as follows: 382 : 383 : 384 : 385 : 386 = 65 : 15 : 65 : 14 : 1, while, those of **6b** from the labeling experiment were as follows: 382 : 383 : 384 : 385 : 386 = 41 : 27 : 47 : 28 : 8. From these results, the D-contents in **6b** were calculated by

$$Br^{79}\ \text{non} : \text{mono} : \text{di-labeled}\ \mathbf{6b} = 41 : 27 - \frac{41}{65} \times 15 : 47 - 41 \qquad (1)$$

$$Br^{81}\ \text{non} : \text{mono} : \text{di-labeled}\ \mathbf{6b} = 41 : 28 - \frac{41}{65} \times 14 : 8 - 1 \qquad (2)$$

Thus, we obtain non- : mono- : di-labeled **6b** = 62.1 ± 1.4% : 27.6 ± 0.6% : 10.3 ± 0.8%. Further, by comparing the intensities of M^+-cyclopentene peaks, the labeled position of **6b** could be defined. In a standard sample, the relative intensities of 314 to 315 (Br^{79}, M^+-cyclopentene) were 100% and 22%, respectively, while in a labeled sample they were 99% and 33%, respectively. Clearly *ca.* 10% D-label was present but *ca.* 30% label was lost by eliminating cyclopentene from the parent molecule. These two figures correspond well with the contents of di- and mono-labeled **6b**. In mono-labeled **6b** D was incorporated predominantly in the cyclopentyl group attached at the 4-position in the ring, while in di-D-

TABLE IV. Mass Spectral Intensities of **6b** in D_2O-Labeling and Standard Experiments

Peak		Labeled **6b** (%)	Standard **6b** (%)
M^+	382	41	65
	382	27	15
	384	47	65
	385	28	14
	386	8	1
M^+-cyclopentene	314	99	100
	315	33	22
	316	100	98
	317	24	18
	318	2	1

TABLE V. Mass Spectral Intensities of **8b** in H_2O^{18}-Labeling and Standard Experiments

Peak M^+	Labeled **8b** (%)	Standard **8b** (%)
396	100	100
397	25.5	26.3
398	109.8	100
397	25.5	24.7
398	9.7	1—2

labeled **6b**, D was incorporated in both the cyclopentyl substituent and the C_4-methine in the ring.

Further, the reaction of **7b** with **5a** in the presence of NEt_3 containing 1 ml of H_2O^{18} (50%) was examined. From the reaction mixture, we obtained **8b** and investigated its O^{18} content (Table V). As is clear from Table V, the O^{18} content in **8b** was calculated to be *ca.* 10% (20%). From these two labeling experiments it was concluded that the source of H in **6** and the source of O in **8** are water which is produced during the reaction (strictly speaking, the H source is **1** and the O source is **5**).

(iv) Ionic Reaction (Not Radical Reaction)

In order to determine the reaction mode, we examined the reaction of **1a** with **5a** in the presence of NEt_3 under an N_2 atmosphere. No inhibition of the formation of **6a** was observed in this run. Further, we examined the reaction under the same reaction conditions but in the presence of 2,4,6-trimethylphenol (radical scavenger 5—25 mmol). In these cases also, formation of **6a** and **8a** was observed in *ca.* 40% yields. From these two results, it can be concluded that the reaction proceeds through an ionic mechanism.

A reaction mechanism which satisfies all the above results is shown in Chart 6 (for **1a** and **5a**). 2,5-Diphenyl-2,4-dihydro-3*H*-pyrazol-3-one (**1a**) was changed to its delocalized anionic state (**1a′** or ion pair with $NHEt_3$) by NEt_3 catalysis. The anion (**1a′**) reacted with cyclopentanone (**5a**) to give an adduct (**12′**), which equilibrated with **12**, **7a** and **12″** under the reaction conditions. In these equilibria, the key step is the production of **12″**. The anion **12″** should be the most stable anion present in these equilibria because **12″** can be delocalized, whereas **12′** can not. The carbanion **12″** attacked the O–H group attached to the cyclopentyl substituent to produce the epoxide **8a** and the resulting H^- was transferred to **7a** to afford the anion **13**. Then the anion **13** abstracted a proton from $\overset{+}{N}HEt_3$ to afford **6a** as the final product.

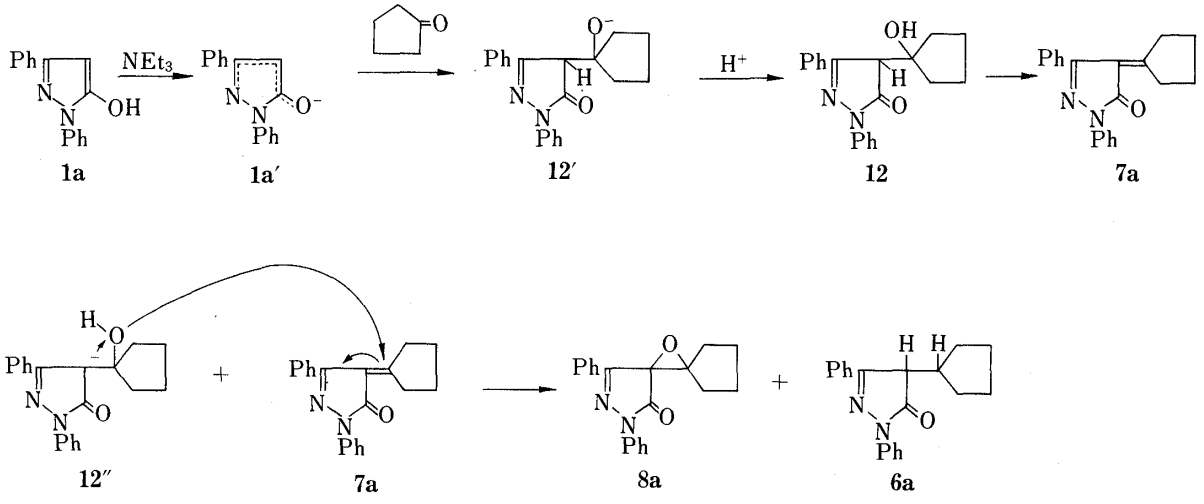


Chart 6

It is true that the D or O^{18} contents in **6b** and **8b** were rather small, but if one takes into account that under the reaction conditions used, **5a** was enolized (the formation of **9a**), and D–H exchange would have occurred through this enol form, the observed D-contents in **6b** are considered to be significant. As for the small O^{18} content in **8b**, we should take account of the back reaction (12→1); if this occurs, H_2O^{18} might be scrambled, which could explain the low but significant O^{18} content in **8b**. A similar type of reaction was reported by Veibel and Linholt.[6] They examined the reaction of 4-alkyl-2,5-diphenyl-2,4-dihydro-3*H*-pyrazol-3-one (**14**) in MeOH containing an excess amount of NEt_3 to yield various 4-alkyl-4-hydroxy-2,5-

diphenyl-2,4-dihydro-3*H*-pyrazol-3-ones (**15**) and $NEt_3(OH)_2$. In these conversions, they explained the formation of **15** in terms of the equilibrium equations shown below.

$$\text{PyRH } (\mathbf{14}) + NEt_3 \rightleftharpoons PyR^- + \overset{+}{N}HEt_3 \qquad (3)$$

$$PyR^- + O_2 \rightleftharpoons PyROO^- \qquad (4)$$

$$2PyROO^- + 2\overset{+}{N}HEt_3 \rightleftharpoons PyROH\text{--}O^-\text{--}HOPyR + Et_3\overset{+}{N}\text{–}O^- \atop \overset{\ }{N}HEt_3^{\,+} \qquad (5)$$

$$PyROH\text{--}O^-\text{--}HOPyR \cdot \overset{+}{N}Et_3 + H_2O \rightleftharpoons 2PyROH\ (\mathbf{15}) + NEt_3(OH)_2 \qquad (6)$$

PyRH = 4-alkyl-2,5-diphenyl-2,4-dihydro-3*H*-pyrazol-3-ones

Under the one set of our reaction conditions (such as **1a** with **5a** in the presence of NEt_3 at room temperature with stirring), we also isolated the 4-hydroxy derivative (**9a**). Thus, it may be reasonable to consider that the formation of **9a** occurs the same reaction mechanism as that proposed by Veibel and Linholt. These considerations strongly support the view that the reaction mechanism affording **6** also involves equilibria such as those shown in Chart 6.

From the synthetic point of view, the observed one-pot cycloalkylation at the 4-position of the 2,4-dihydro-3*H*-pyrazol-3-one ring is valuable. Although base-catalyzed[7)] and acid-catalyzed[8)] alkylations of 2-substituted 2,4-dihydro-3*H*-pyrazol-3-one rings and base-catalyzed condensation[9)] of alkylhydrazines with α-cycloalkyl-β-keto esters may be applied for the synthesis of 4-cycloalkyl-2,4-dihydro-3*H*-pyrazol-3-ones, these methods are troublesome and give poor results. However, by using our method, one could easily obtain 4-cycloalkyl-2,4-dihydro-3*H*-pyrazol-3-ones under mild reaction conditions.

Further studies to extend the scope of the above conversions to other heterocycles are in progress in this laboratory.

Experimental

All melting points were recorded on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were

TABLE VI. Physical Properties of 2-Aryl-4-cyclopentylidene-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-ones (**7**)

Compd. No.	Ar	^{1}H-NMR δ ($CDCl_3$)	IR ν_{KBr} cm^{-1}	UV $\varepsilon_{max}^{ethanol}$ nm (log ε)	MS *m/e* (Rel. intensity)
7a	Ph	1.55—1.65 (m, 2H)	2950	260 (4.15)	302 (M^+, 100)
		1.70—1.85 (m, 2H)	1695		273 (25)
		2.10 (t, 2H, *J*=7.3 Hz)	1630		
		3.18 (t, 2H, *J*=7.3 Hz)	1600		
		7.11—7.50 (m, 8H)			
		7.90—8.10 (m, 2H)			
7b	4-Br–Ph	1.63 (t of t, 2H, *J*=7, 7.3 Hz)	2960	268 (4.27)	382, 380 (M^+, 98,
		1.80 (t of t, 2H, *J*=7, 7.3 Hz)	1685		100)
		2.39 (t, 2H, *J*=7 Hz) 3.19 (t, 2H,	1635		353, 351 (25, 25)
		J=7 Hz) 7.24—7.53 (m, 7H)	1590		
		7.94 (d, 2H, *J*=9 Hz)			
7c	4-Cl–Ph	1.64 (t of t, 2H, *J*=7, 7.3 Hz)	2960	263 (4.30)	338, 336 (M^+, 35,
		1.81 (t of t, 2H, *J*=7, 7.3 Hz)	1680		100)
		2.38 (t, 2H, *J*=7 Hz) 3.20 (t, 2H,	1640		309, 307 (10, 30)
		J=7 Hz) 7.34 (d, 2H, *J*=8.8 Hz)	1590		
		7.45—7.50 (s like 5H)			
		7.99 (d, 2H, *J*=8.8 Hz)			

measured with a Jasco A-3 spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra (^{1}H-NMR 199.50 MHz and ^{13}C-NMR 50.10 MHz) were recorded on a JEOL JNM-FX-200 spectrometer with tetramethylsilane as an internal standard. The following abbreviations are used: s=singlet, d=doublet, t=triplet, m=multiplet. Ultraviolet (UV) spectra were recorded with a Shimadzu UV-300 spectrometer. Mass spectra were recorded with a Hitachi MU-7MG spectrometer.

Column chromatography was carried out on Kiesel gel 60 (70—230 mesh) or neutral alumina (A 2147 sigma) with benzene as an eluent.

General Procedure for the Preparation of 2,5-Diaryl-4-cyclopentylidene-2,4-dihydro-3*H*-pyrazol-3-ones (7)——A solution of 2,5-diaryl-2,4-dihydro-3*H*-pyrazol-3-one (**1**, 0.01 mol) in 100 ml of dry cyclopentanone (**5a**) was refluxed

TABLE VII. Physical Properties of 2-Aryl-4-cycloalkyl-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-ones (**6**)

Compd. No.	Ar	R	^{1}H-NMR δ ($CDCl_3$)	IR ν_{KBr} cm^{-1}	UV $\varepsilon_{max}^{ethanol}$ nm (log ε)	MS *m/e* (Rel. intensity)
		Cyclopentyl	1.19—2.10 (m, 9H) 3.71 (d, 1H, J=4 Hz) 7.16—8.10 (m, 10H)	3450 2960 1610 1585	266 (4.25)	304 (M^+, 55) 236 (100)
		Cyclopentyl	1.08—2.20 (m, 9H) 3.74 (d, 1H, J=4.2 Hz) 7.50—7.93 (m, 9H)	3430 2960 1600 1590	266 (4.28)	384, 382 (M^+, 45, 45) 316, 314 (99, 100)
		Cyclopentyl	1.20—2.23 (m, 9H) 3.70 (d, 1H, J=4 Hz) 7.23—8.10 (m, 9H)	3450 2960 1605 1585 1565	270 (4.25)	340, 338 (M^+, 18, 60) 272, 270 (40, 100)
		Cyclohexyl	1.08—2.16 (m, 11H) 3.70 (d, 1H, J=3 Hz) 7.16—8.01 (m, 10H)	3450 2920 1605 1580 1560	265 (4.20)	318 (M^+, 60) 236 (100)
		Cyclohexyl	1.05—2.18 (m, 11H) 3.70 (d, 1H, J=3 Hz) 7.50—7.98 (m, 9H)	3430 2920 1605 1580 1570	265 (4.20)	398, 396 (M^+, 52, 50) 316, 314 (95, 100)
		Cyclohexyl	1.11—2.16 (m, 11H) 3.69 (d, 1H, J=3 Hz) 7.35—7.99 (m, 9H)	3430 2930 1600 1580 1570	270 (4.18)	354, 352 (M^+, 13, 33) 272, 270 (33, 100)
		Cycloheptyl	1.19—1.77 (m, 12H) 2.00—2.20 (m, 1H) 3.71 (d, 1H, J=3 Hz) 7.17—8.00 (m, 9H)	3450 2920 1605 1590 1570	263 (4.22)	332 (M^+, 60) 236 (100)
		Cycloheptyl	1.08—2.21 (m, 13H) 3.72 (d, 1H, J=3.5 Hz) 7.51—8.07 (m, 9H)	3450 2920 1600 1580 1560	265 (4.22)	412, 410 (M^+, 40, 35) 316, 314 (95, 100)
		Cycloheptyl	1.20—2.20 (m, 13H) 3.70 (d, 1H, J=2.5 Hz) 7.20—8.00 (m, 9H)	3420 2910 1600 1580 1560	268 (4.23)	368, 366 (M^+, 12, 30) 272, 270 (42, 100)

TABLE VIII. Physical Properties of 2-Aryl-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-one-4-cyclopentylidene Epoxides (**8**)

Compd.	Ar	^{1}H-NMR δ ($CDCl_3$)	IR ν_{KBr} cm^{-1}	UV $\varepsilon_{max}^{ethanol}$ nm (log ε)	MS *m/e* (Rel. intensity)
8a	Phenyl	1.88—2.20 (m, 8H) 7.17—8.03 (m, 10H)	2920 1715 1600 1500 1310 1260	260 (4.22)	318 (M^+, 100) 235 (12)
8b	4-Br-Ph	1.50—2.20 (m, 8H) 7.30—8.10 (m, 9H)	2930 1725 1600 1490 1310 1260	261 (4.25)	398, 396 (M^+, 98, 100) 315, 313 (30, 28)
8c	4-Cl-Ph	1.49—2.30 (m, 8H) 7.39 (d, 2H, J=9 Hz) 7.40—7.85 (m, 5H) 7.93 (d, 2H, J=9 Hz)	2930 1725 1600 1490 1300 1250	262 (4.26)	354, 352 (M^+, 40, 100) 271, 269 (10, 35)

for 8 h. The reaction mixture was evaporated *in vacuo* at room temperature to give a dark brown solid, which was recrystallized from iso-PrOH to give the corresponding 4-cyclopentylidene-2,5-diaryl-2,4-dihydro-3*H*-pyrazol-3-one (**7**) in high yield.

General Procedure for the Preparation of 4-Cycloalkyl-2,5-diaryl-2,4-dihydro-3*H*-pyrazol-3-ones (6b—i)——A solution of 2,5-diaryl-2,4-dihydro-3*H*-pyrazol-3-one (**1**, 0.01 mol) in dry cycloalkanone (**5**, 100 ml) containing 0.1 mol of NEt_3 was refluxed for 12 h. The reaction mixture was evaporated *in vacuo* at room temperature to give a dark brown oily residue, which was dissolved in 10 ml of dry benzene. The solution was allowed to stand overnight at 5 °C. The resulting white precipitate was obtained and recrystallized from iso-PrOH to give **6** as white needles.

Preparation of 4-Cyclopentyl-2,5-diphenyl-2,4-dihydro-3*H*-pyrazol-3-one (6a)——A solution of 2,5-diphenyl-2,4-dihydro-3*H*-pyrazol-3-one (**1a**, 0.01 mol) in 100 ml of dry cyclopentanone containing 0.1 mol of NEt_3 was refluxed for 12 h. The reaction mixture was evaporated *in vacuo* at room temperature to give a dark brown oily residue, which was chromatographed on silica gel with benzene as an eluent to give crude **6a**. Recrystallization **6a** from iso-PrOH gave analytically pure **6a** as white needles.

General Procedure for the Isolation of 2,5-Diaryl-2,4-dihydro-3*H*-pyrazol-3-one-4-cyclopentylidene Epoxides (8)——A solution of 2,5-diaryl-2,4-dihydro-3*H*-pyrazol-3-one (**1**, 0.01 mol) in 100 ml of dry cyclopentanone (**5a**) containing 0.1 mol of NEt_3 was refluxed for 12 h. The reaction mixture was evaporated *in vacuo* at room temperature to afford a dark brown oily residue, which was chromatographed on neutral alumina with benzene as an eluent. From the first fraction, **8** was obtained as a white powder, which was recrystallized from dry acetone to give analytically pure **8** as white crystals. From the second fraction **6** was obtained.

Reaction of 2,5-Diphenyl-2,4-dihydro-3*H*-pyrazol-3-one (1a) with Cyclopentanone (5a) in the Presence of NEt_3 at Room Temperature——A solution of **1a** (0.01 mol) in dry cyclopentanone (**5a**, 100 ml) containing 0.1 mol of NEt_3 was stirred at room temperature for 24 h. The reaction mixture was then evaporated *in vacuo* at room temperature to give a drak brown oily residue, which was chromatographed on neutral alumina with benzene as an eluent. From the first fraction, the epoxide **8a** was obtained in 43% yield, from the second fraction the other oxidized product, 4-(2-oxocyclopentyl)-4-hydroxy-2,5-diphenyl-2,4-dihydro-3*H*-pyrazol-3-one (**9a**, 0.79 g) was obtained in 23% yield.

9a: mp 172—174 °C; ^{1}H-NMR ($CDCl_3$) δ 1.32—1.93 (m, 4H), 2.13—2.40 (m, 2H), 2.73 (dd, 1H, J=10.91, 13.54 Hz), 6.09 (1H, OH), 7.17—7.48 (m, 6H), 7.96 (dd, 2H, J=8.3, 1.2 Hz), 8.12 (dd, 2H, J=8.3, 7.3 Hz); ^{13}C-NMR ($CDCl_3$) δ 220.24 (s), 172.11 (s), 155.52 (s), 137.63 (s), 130.95 (d), 129.56 (s), 128.94 (d, 4C), 127.10 (d, 2C), 125.57 (d), 118.89 (d, 2C), 82.03 (s), 49.67 (d), 39.72 (t), 24.39 (t), 20.37 (t); IR (KBr) 3480, 2950, 1725, 1690, 1600 cm^{-1}; UV $\varepsilon_{max}^{ethanol}$ nm (log ε) 263 (4.22); MS *m/e* (rel. inten.) 334 (M^+, 62), 218 (100). *Anal.* Calcd for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38. Found C, 72.02; H, 5.19; N, 8.15.

Reaction of 2,5-Diphenyl-2,4-dihydro-3*H*-pyrazol-3-one (1a) with 5a in the Presence of NEt_3 and 2,4,6-Trimethylphenol under an N_2 Atmosphere——A solution of **1a** (0.01 mol) in 100 ml of dry cyclopentanone (**5a**) containing 0.1 mol of NEt_3 and 2,4,6-trimethylphenol (2.04 g, 0.015 mol) was refluxed for 12 h under an N_2 atmosphere. The reaction mixture was evaporated *in vacuo* at room temperature to leave a semi-solid residue, which was chromatographed on silica gel with benzene as an eluent. From the first fraction, 2,4,6-trimethylphenol (1.92 g) was obtained. From the second fraction, **6a** (1.10 g, 36%) was obtained as white needles. When the amount of 2,4,6-trimethylphenol was changed to 0.005, 0.010, 0.020 and 0.025 mol, **6a** was obtained in 33, 38, 34 and 36% yields, respectively.

Reaction of 2-(4-Bromophenyl)-4-cyclopentylidene-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (7b) with Cyclopentanone (5a) at Reflux in the Presence of NEt_3 Containing 1 ml of D_2O——A solution of **7b** (0.01 mol) in 100 ml of dry cyclopentanone (**5a**) containing 0.1 mol of NEt_3 and 1 ml of D_2O was refluxed for 12 h. The reaction mixture was evaporated *in vacuo* at room temperature to leave a dark brown oily residue, which was dissolved in

TABLE IX. ^{13}C-NMR Data for 2-Aryl-4-cyclopentylidene-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-ones (**7**) in $CDCl_3$

Compd. No.	δ values from tetramethylsilane
7a	173.86 (s), 163.56 (s), 151.01 (s), 138.73 (s), 133.50 (s), 129.31 (d), 128.83 (d, 2C), 128.68 (d, 2C), 124.48 (d, 2C), 124.71 (d), 121.72 (s), 119.02 (d, 2C), 36.51 (t), 35.15 (t), 25.86 (t), 25.32 (t)
7b	180.61 (s), 164.56 (s), 152.42 (s), 138.87 (s), 134.35 (s), 132.74 (d, 2C), 130.53 (d), 129.82 (d, 2C), 129.60 (d, 2C), 121.90 (s), 121.35 (d, 2C), 118.54 (s), 37.63 (t), 36.29 (t), 26.93 (t), 26.03 (t)
7c	179.32 (s), 163.37 (s), 151.23 (s), 137.44 (s), 133.27 (s), 129.38 (d), 128.77 (d, 2C), 128.65 (d, 2C), 128.45 (d, 2C), 126.81 (s), 121.47 (s), 119.81 (d, 2C), 36.53 (t), 35.19 (t), 25.81 (t), 25.26 (t)

TABLE X. ^{13}C-NMR Data for 2-Aryl-4-cycloalkyl-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-ones (**6**)

Compd. No.	δ values from tetramethylsilane
6a	172.92 (s), 158.88 (s), 138.13 (s), 131.03 (s), 130.20 (d), 128.72 (d, 4C), 126.72 (d, 2C), 125.00 (d), 119.10 (d, 2C), 51.52 (d), 41.00 (d), 28.24 (t), 27.83 (t), 24.98 (t, 2C)
6b	173.05 (s), 159.40 (s), 137.41 (s), 131.89 (d, 2C), 131.06 (s), 130.53 (d), 128.95 (d, 2C), 126.90 (d, 2C), 120.53 (d, 2C), 118.00 (s), 51.72 (d), 41.08 (d), 28.36 (t), 27.95 (t), 25.03 (t, 2C)
6c	172.93 (s), 159.28 (s), 136.80 (s), 130.67 (s), 130.48 (d), 130.14 (s), 128.87 (d, 2C), 128.83 (d, 2C), 126.81 (d, 2C), 120.09 (d, 2C), 51.52 (d), 40.99 (d), 28.24 (t), 27.83 (t), 24.96 (t, 2C)
6d	172.85 (s), 158.22 (s), 138.10 (s), 131.01 (s), 130.20 (d), 128.77 (d, 2C), 128.70 (d, 2C), 126.70 (d, 2C), 124.98 (d), 119.05 (d, 2C), 54.97 (d), 40.44 (d), 29.48 (t), 28.16 (t), 26.61 (t), 26.22 (t), 25.71 (t)
6e	172.98 (s), 158.75 (s), 137.34 (s), 131.84 (d, 2C), 130.94 (s), 130.55 (d), 128.95 (d, 2C), 126.88 (d, 2C), 120.46 (d, 2C), 117.95 (s), 55.07 (d), 40.50 (d), 29.55 (t), 28.22 (t), 26.64 (t), 26.25 (t), 25.71 (t)
6f	172.78 (s), 158.54 (s), 136.69 (s), 130.79 (s), 130.40 (d), 130.11 (s), 128.82 (d, 2C), 128.77 (d, 2C), 126.75 (d, 2C), 120.02 (d, 2C), 54.59 (d), 40.44 (d), 29.50 (t), 28.14 (t), 26.59 (t), 26.20 (t), 25.69 (t)
6g	173.00 (s), 159.40 (s), 138.13 (s), 130.98 (s), 130.18 (d), 128.77 (d, 2C), 128.70 (d, 2C), 126.70 (d, 2C), 125.00 (d), 119.05 (d, 2C), 55.84 (d), 42.04 (d), 32.17 (t), 29.60 (t), 27.78 (t), 27.27 (t), 27.00 (t), 26.63 (t)
6h	173.12 (s), 158.94 (s), 137.41 (s), 131.87 (d, 2C), 130.97 (s), 130.53 (d), 128.97 (d, 2C), 126.90 (d, 2C), 120.51 (d, 2C), 117.98 (s), 55.97 (d), 42.13 (d), 32.25 (t), 29.65 (t), 27.80 (t), 27.32 (t), 27.05 (t), 26.66 (t)
6i	172.92 (s), 158.76 (s), 136.74 (s), 130.81 (s), 130.37 (d), 130.16 (s), 128.84 (d, 2C), 128.77 (d, 2C), 126.75 (d, 2C), 120.07 (d, 2C), 55.89 (d), 42.09 (d), 32.20 (t), 29.57 (t), 27.78 (t), 27.27 (t), 27.00 (t), 26.61 (t)

TABLE XI. ^{13}C-NMR Data for 2-Aryl-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-one-4-cyclopentylidene-epoxides (**8**)

Compd. No.	δ values from tetramethylsilane
8a	167.55 (s), 154.76 (s), 138.38 (s), 131.14 (s), 130.52 (d), 128.92 (d, 2C), 128.51 (d, 2C), 127.16 (d, 2C), 125.41 (d), 118.76 (d, 2C), 80.33 (s), 66.28 (s), 31.16 (t), 30.22 (t), 25.46 (t), 24.44 (t)
8b	167.55 (s), 155.19 (s), 137.68 (s), 131.99 (d, 2C), 131.18 (s), 130.72 (d), 128.61 (d, 2C), 127.29 (d, 2C), 120.21 (d, 2C), 118.37 (s), 80.59 (s), 66.31 (s), 31.18 (t), 30.28 (t), 25.47 (t), 24.40 (t)
8c	167.44 (s), 155.10 (s), 137.10 (s), 131.18 (s), 130.40 (d), 128.88 (d, 2C), 128.53 (d, 2C), 127.19 (d, 2C), 119.75 (d, 2C), 80.42 (s), 66.30 (s), 31.14 (t), 30.24 (t), 25.45 (t), 24.40 (t)

10 ml of dry benzene. The solution was kept overnight at 5 °C. From the benzene solution, 2-(4-bromophenyl)-4-cyclopentyl-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (**6b**, 34%) was obtained as white precipitate. Mass spectral data for this white precipitate are listed in Table IV.

Reaction of 2-(4-Bromophenyl)-4-cyclopentylidene-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (7b) with Cyclopentanone (5a) at Reflux in the Presence of NEt_3 Containing 1 ml of H_2O^{18}——A solution of **7b** (0.01 mol) in 100 ml of dry cyclopentanone containing 0.1 mol of NEt_3 and 1 ml of H_2O^{18} was refluxed for 12 h. The reaction mixture was evaporated *in vacuo* at room temperature to leave a dark brown oily residue, which was chromatographed on neutral alumina with benzene as an eluent. From the first fraction, the epoxide **8b** (1.43 g, 36%) was

obtained. After recrystallization of **8b** from acetone, the mass spectrum was measured; the results are listed in Table V.

References and Notes

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