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The synthesis and spectral characteristics of a bis-spiro compound: 2,6-bis(4-phenyl-3- $\Delta^1$ -pyrazolinyl)cyclohexanone are reported. Unlike literature reports, this particular  $\Delta^1$ -pyrazoline does not readily rearrange to the  $\delta^2$  isomer on heating. Pyrolysis gives 2,6-bis( $\alpha$ -methylbenzylidene)cyclohexanone. A monopyrazolinylketone was also isolated which is most likely an intermediate in the bis-denitrogenation. A mechanism for the denitrogenation-rearrangement is proposed.

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## Results and Discussion.

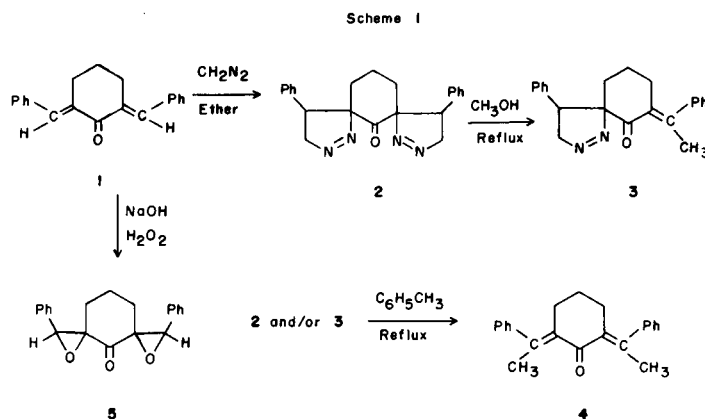
The reaction of mono- and diarylidenecycloalkanones with hydrazine hydrate was studied by Oszbach and Szabo [1] who reported that with 2,6-diarylidenecyclohexanones the reaction afforded bicyclic pyrazolines. Later, Khalaf and coworkers [2] reported that refluxing 2,6-diarylidenecyclohexanones with hydrazine hydrate in methanol led to the formation of a bicyclic pyrazoline. We wish to report a bis-pyrazolinylketone which has been shown to possess mutagenic activity [3]. The pyrolysis products of this compound are discussed.

### I) The Chemistry of Pyrazolinylketones.

Reaction of diazomethane with 2,6-dibenzylidenecyclohexanone (**1**) forms 2,6-bis(4-phenyl-3- $\Delta^1$ -pyrazolinyl)cyclohexanone (**2**). The  $\Delta^1$ -pyrazoline structure was indicated by the lack of an -NH absorption band near  $3400\text{ cm}^{-1}$  and the presence of a -N=N- absorption at  $1555\text{ cm}^{-1}$  in the infrared spectrum. The direction of the addition of diazomethane to the double bond is assumed to be that demonstrated for alkene linkage having other adjacent electron-withdrawing groups [4], *i.e.* with the carbon of diazomethane attacking *beta* to the cyclohexanone carbonyl.

Siato, Giichi and coworkers reported that  $\Delta^1$ -3-acetyl-4-arylpyrazolines are unstable and isomerize to the  $\Delta^2$  isomers on recrystallization [5]. They also reported cycloaddition of 3-(4R-phenyl)-1-phenyl-2-propen-1-one with diazomethane gave  $\Delta^1$ -pyrazolines which isomerize to  $\Delta^2$ -isomers on heating in methanol [6]. Indeed, our MM2 calculation showed a markedly greater stability of the  $\Delta^2$ -structure over the  $\Delta^1$ -pyrazoline. The attempt to synthesize the  $\Delta^2$ -isomer by heating compound **2** in methanol failed. Denitrogenation on one side of the molecule was found instead of isomerization. The product thus found is 2-( $\alpha$ -methylbenzylidene)-6-(4-phenyl-3- $\Delta^1$ -pyrazolinyl)cyclohexanone (**3**). The structure of compound **3** was indicated by the presence of a methyl group in the nmr spectrum. Further heating of **3** using toluene as the solvent leads to the formation of 2,6-bis( $\alpha$ -methylbenzylidene)cyclohexanone

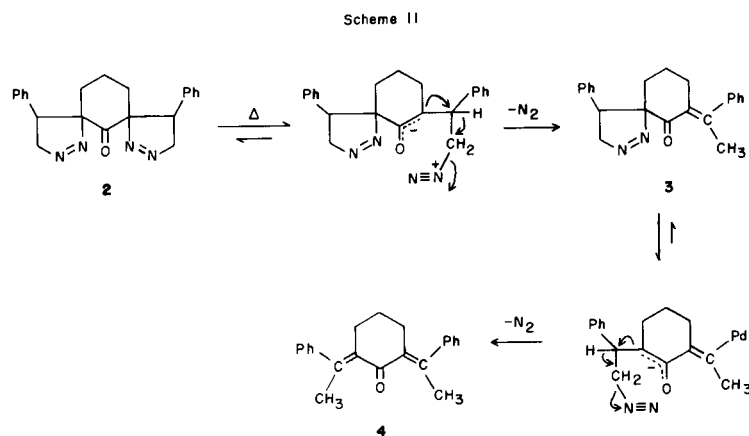
(**4**). The denitrogenation was indicated by the presence of methyl groups in the nmr spectrum instead of methylene groups and the lack of -N=N- absorptions in the ir spectrum.



Literature reports [7] indicate that the pyrolysis or photolysis products of a pyrazoline generally are cyclopropane derivatives or a mixture of a cyclopropane and an alkene. However, in our case, the only pyrolysis products are alkenes **3** or **4**. No cyclopropane derivative has been detected. Three-membered rings have a great deal of angle strain, since  $\sim 75^\circ$  interorbital angles represent a large departure from the tetrahedral angles. If either bis- or monocyclopropylcyclohexanone existed, the endocyclic bond angles at C2 and C6 of the cyclohexanone ring must increase from  $109^\circ$ , but, this possibility is restricted by the ring. The mechanism for this pyrolysis process is postulated as shown in Scheme II. An analogous radical process is an alternative possibility.

### II) Spectral Properties of the Pyrazolinylketones.

In 1969, Matter, Pascual and coworkers [8,9] reported a method which can be used to estimate the chemical shifts of olefinic protons. We found, by following their method, that the chemical shift of the olefinic proton of *E*-isomer of



2,6-dibenzylidene-cyclohexanone (**1**) is 7.47 ppm and that of the *Z*-isomer is 7.25 ppm. The actual chemical shift, from Sadtler indices, is 7.76 ppm. It is clear that compound **1** exists as its *E*-isomer with the phenyl group *trans* to the carbonyl group. Compound **2** is the product of concerted cycloaddition of compound **1** so both of them most likely have the same *trans* configuration. MM2 calculations showed a greater stability of the *E*-isomer.

The nmr spectra of the pyrazolines, listed in Table I, are well resolved and informative. As has been observed by McGreer [10,11] and Crawford [12], the nmr spectra have distinct geometrical implications. Models suggest that the phenyl group in the  $\Delta^1$ -pyrazoline ring should be *trans* to the carbonyl group of the cyclohexanone, (Scheme III). From McGreer's report [10,11], the chemical shift of the C4 hydrogen in *cis*-3,5-dimethyl-3-carbomethoxy- $\Delta^1$ -pyrazoline (**6**) gave absorptions at  $\delta$  3.32 and 0.86, which were from hydrogen *cis* and *trans* to the carbonyl group. The C4 hydrogen on the pyrazolinyl ring of compounds **2** and **3** appears at 3.88 which can thus be assigned *cis* to the carbonyl group.

In compounds **2** and **3** if the phenyl group is *trans* to the carbonyl group, it should produce a shielding effect of the cyclohexanone ring protons, C3 and C5 as models as well as molecular mechanics calculations show that those ring protons lie over the face of phenyl. The nmr spectrum of the 2,6-dibenzal-cyclohexanone bisepoxide [13] shows that the four hydrogens of C3 and C5 have chemical shifts of 1.5 and 1.65 ppm (compared to 1.89 in cyclohexanone itself), consistent with the suggestion that these hydrogens are shielded by the phenyl group. In compound **2**, the proton chemical shifts at C3 and C5 of the cyclohexanone ring are 1.75 and 1.84 ppm, also consistent with a shielding effect by the phenyl group. The greater flexibility of the five-membered ring enables phenyl to be further removed from the C3 equatorial hydrogen. Thus, the shielding effect is attenuated. MM2 calculations indicate a greater stability of the phenyls *trans* to carbonyl than phenyls *cis* to carbonyl. In the latter, both phenyls are canted toward

-C=O, resulting in a severe repulsion effect also easily seen in molecular models. In compound **4** the Lanthanide induced shift (LIS) effect is greater on methyl than phenyl. Since the (Europium is complexed to carbonyl, this indicated that methyl is *cis* to carbonyl.

Scheme III

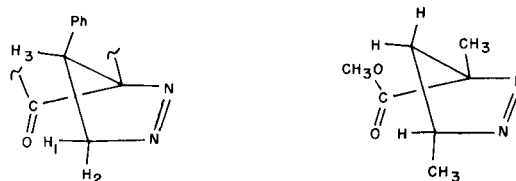


Table I

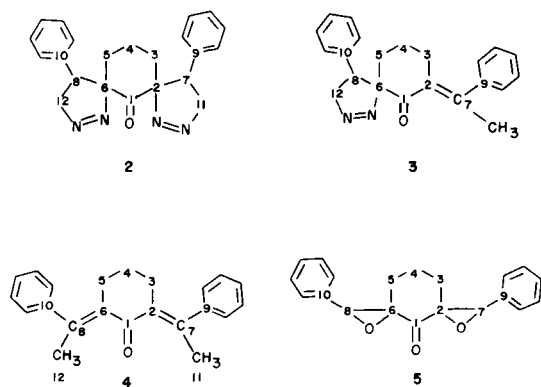
Coupling Constants and Chemical Shifts for Pyrazolines Displaying AB Spectra at C5

Compound	Coupling Constants, Hz	Chemical Shifts, ppm
<b>2</b>	$J_{12} = -18.0$	H1 = 4.66
	$J_{13} = 8.06$	H2 = 5.00
	$J_{23} = 3.2$	H3 = 3.88
<b>3</b>	$J_{12} = -17.94$	H1 = 4.85
	$J_{13} = 8.50$	H2 = 4.97
	$J_{23} = 3.94$	H3 = 3.89

The infrared spectrum of the bis-pyrazoline **2** displays the -N=N-stretching frequency at  $1555\text{ cm}^{-1}$  which is the standard ir absorption position [14]. The ir spectrum of the monopyrzoline **3** shows the -N=N-stretching frequency at  $1542\text{ cm}^{-1}$ . The lower frequency is probably due to a slight lengthening of the double bond.

### III) The $^{13}\text{C}$ Study.

Marshall and Seiwel have reported that a larger  $^3J_{\text{CH}}$  value (14.5 Hz) is found between carbonyl and *trans* hydrogen and a smaller value (6.8 Hz) is found for *cis* nuclei [15]. Later, Kingsbury *et al.* [16] reported, in a table summary,



that the  $^3J_{CH}$  of an olefinic proton *cis* to a carbonyl group is 4.3-10.0 Hz compared to that of a *trans* nuclei which has the value of 9.5-16.9 Hz. We calculated the  $^3J_{CH}$  value of compound **1** and found it is 6.6 Hz which proves that **1** has olefinic protons *cis* to the carbonyl group.

The  $^{13}C$  spectral study shows that the  $-N=C$  of a  $\Delta^2$  pyrazoline always has a chemical shift around 150 ppm or higher [17,18]. Our  $^{13}C$  spectra of compounds **2** and **3** have no chemical shift in that area. This is strong evidence that both of compounds **2** and **3** are  $\Delta^1$ -isomers. We used Touillaux and coworkers' [19] results as the reference to assign the  $^{13}C$  chemical shift of compound **2**. It calls our attention to assign the chemical shift of compound **3** which shows for peaks between 133 ppm to 146. No doubt those four peaks should be the composition of two *ipso*-carbons of the phenyl group and two alkene carbons. Since compound **3** contains both the pyrazoline and alkene properties, it is not too difficult to assign those four peaks. The  $^{13}C$  chemical shift of compound **4** is easy to obtain by comparing it with the compound **1** [20]. The  $^{13}C$  chemical shifts of compounds **2**, **3**, **4**, and **5** are shown in Table II.

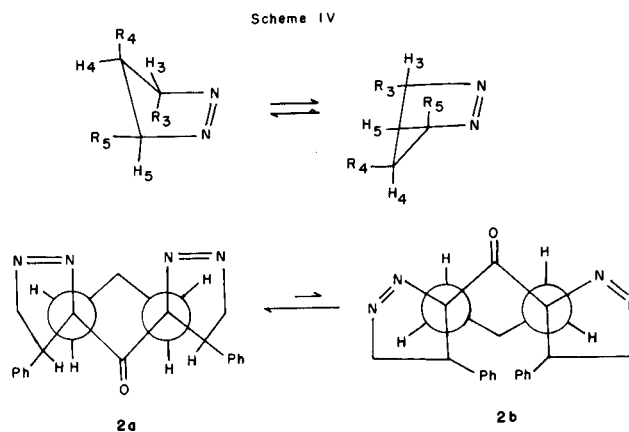
Table II  
 $^{13}C$  Chemical Shifts [21] of **2**, **3**, **4**, and **5**

Carbon	2	3	4	5
1	198.0	198.4	200.0	203.1
2	103.6	142.3	143.3	66.2
3	31.2	32.5	30.8	26.1
4	18.3	22.7	24.6	19.4
5	31.2	31.6	30.8	26.1
6	103.6	105.0	143.3	66.2
7	42.8	145.2	143.3	65.5
8	42.8	42.3	143.3	65.5
9	137.7	133.7	136.1	133.1
10	137.7	138.4	136.1	133.1
11	83.8	22.1	22.7	
12	83.8	83.8	22.7	

#### IV) The Conformation Study.

As pointed out by Gulbrandersen and Kolsaker [22] the  $\Delta^1$ -pyrazoline ring system equilibrates in solution between

the two conformations, where pseudoaxial and equatorial positions are rapidly interchanging (Scheme IV). Generally the conformer with the highest number of groups in the pseudoequatorial positions will be the most stable. Since compound **2** contains 3 rings, the movement of the pyrazoline ring will be restricted by the cyclohexanone ring. This will result in a more limited conformational isomer of compound **2**. Are the azo groups in the pseudoaxial or equatorial positions of the cyclohexanone ring? From the steric hindrance point of view, one could predict that the carbonyl group and phenyl group of 2,6-dibenzylidene-cyclohexanone would be *trans* to each other. The *E*-conformation of **1** was suggested by the MM2 energy calculation. The energy calculations shows that the *E*-isomer has about 30 Kcal/mole of steric energy compared to 55 Kcal/mole steric energy for the *Z*-isomer. By the model study, we find that the azo group must be in the pseudoaxial position of the cyclohexanone ring. If the azo group is in the equatorial position then the steric hindrance between axial protons and axial CH-Ph groups will destabilize the total ring system. This assumption agrees with the result of an MM2 calculation. The MM2 calculation indicates that **2a**, with its azo group in the pseudoaxial position of the cyclohexanone ring, has about 34.8 Kcal/mole steric energy compared to 48.2 Kcal/mole steric energy for the **2b**. Its data are in accord with the axial  $-N=N-$  structure [23].



#### EXPERIMENTAL

Melting points were determined with a Mel-Temp capillary melting point apparatus and are uncorrected. Elemental analyses were performed by the Micro Tech Laboratory, Skokie, Illinois.

Spectra were obtained in reagent grade chloroform-*d* employing tetramethylsilane as an internal standard. The recording instruments were a Varian EM-390 or XL-200 spectrometer. The carbon-13 magnetic resonance spectra were determined in chloroform-*d* solution employing a Varian XL-200 spectrometer. Chemical shifts are referenced to internal chloroform-*d* taken as 76.9 ppm downfield from tetramethylsilane and are accurate to 0.1 ppm. The  $^1H$  and  $^{13}C$  nmr spectra of compounds **2** and **3** were performed by the Colorado State University NMR Regional Center. Infrared spectra were obtained on a Beckman model Acculab 4

grating spectrophotometer or a Perkin-Elmer model 283 grating instrument. The high resolution mass spectra were determined by an AEI mass Spectrometer Model 50-76 equipped with a DS-30 data system. The mode of analysis was electron impact by direct insertion of sample. Ultraviolet spectra were obtained using a Hewlett-Packard 8450A UV/Vis spectrophotometer with anhydrous methanol as solvent.

#### 2,6-Dibenzylidene-cyclohexanone (1).

This compound was obtained by the method of Garland and Reid [24] but more details will be given here. A solution which contained 212 g (2 moles) of benzaldehyde in 230 g (5 moles) of ethanol was added to a 2 liter flask which contained 98 g (1 mole) of cyclohexanone. Then 100 ml of 10% (w/w) of sodium hydroxide was added slowly. The mixture then stood overnight. The crude orange-colored product was recrystallized from glacial acetic acid to obtain 202 g of yellow product (74%), mp 117-118°.

#### 2,6-bis(4-Phenyl-3- $\Delta^1$ -pyrazolinyl)cyclohexanone (2).

An ether solution which contained 3.0 g of diazomethane, prepared by potassium hydroxide hydrolysis of *p*-tolylsulfonylethylmethylnitrosoamide ("Diazald", Aldrich Chemical Company), was distilled directly into a stirred and externally cooled solution which contained 9.0 g (0.033 mole) of **1** in 50 ml of ether. After addition was complete, stirring was continued at room temperature until the solution turned colorless (generally it takes 1 to 2 days). The solution was then put in the ice-chest overnight. After separation from the ether solution, 10.3 g of pyrazoline was obtained. The filtrate ether solution was evaporated to obtain light yellow crystals which were recrystallized by using a minimum amount of anhydrous ether to get 0.7 g of the second crop. The total yield was 11.0 g (94%), mp 123°; ir (chloroform): 1709  $\text{cm}^{-1}$  (C=O), 1555  $\text{cm}^{-1}$  (N=N-); uv (methanol): 330 nm, 278 nm; nmr (deuteriochloroform):  $\delta$  7.0-7.25 (m, 10, Ph), 5.01-4.67 (q, 4, -CH<sub>2</sub>), 3.88 (q, 2, -C-H), 1.7-2.2 (m, 6, -(CH<sub>2</sub>)<sub>3</sub>); ms: (70 eV); m/e Calcd. for C<sub>22</sub>H<sub>22</sub>N<sub>4</sub>O: 358.179, Found: 330.175 (no molecular ion observed; loses one molecule of nitrogen).

Anal. Calcd. for C<sub>22</sub>H<sub>22</sub>N<sub>4</sub>O: C, 73.72; H, 6.18; N, 15.63. Found: C, 73.82; H, 6.18; N, 15.83.

#### 2-( $\alpha$ -Methylbenzylidene)-6-(4-phenyl-3- $\Delta^1$ -pyrazolinyl)cyclohexanone (3).

A mixture which contained 10.0 g of **2** in 100 ml of methanol was refluxed overnight. The solvent was then evaporated and the residue was extracted with petroleum ether. The pet ether solution was then cooled in the ice-chest overnight. Filtration gave 7.0 g (76%) of white crystals, mp 86°; ir (chloroform): 1682  $\text{cm}^{-1}$  (C=O), 1542  $\text{cm}^{-1}$  (N=N-); uv (methanol): 282 nm; nmr (deuteriochloroform):  $\delta$  6.9-7.4 (m, 10, Ph), 4.97-4.85 (q, 2, -CH<sub>2</sub>), 3.89 (q, 1, -CH), 1.47-1.89 (c, 6, -(CH<sub>2</sub>)<sub>3</sub>); ms (70 eV), m/e Calcd. for C<sub>22</sub>H<sub>22</sub>N<sub>2</sub>O: 330.173, Found: 330.175.

Anal. Calcd. for C<sub>22</sub>H<sub>22</sub>N<sub>2</sub>O: C, 79.97; H, 6.71; N, 8.48. Found: C, 79.84; H, 6.81; N, 8.68.

#### 2,6-bis( $\alpha$ -Methylbenzylidene)cyclohexanone (4).

A mixture which contained 10.0 g of **3** in 100 ml of toluene was refluxed overnight. After evaporating two-thirds of the solvent, the residue solution was chromatographed on silica gel with 1:2 ratio of benzene and petroleum ether solution as eluent. Most of solvent was first evaporated by using a rotatory evaporator and then a high vacuum pump was applied to evaporate all of the solvent to obtain 7.5 g (89%) of **4** as yellow crystals. For analysis purposes, the product can be recrystallized by using ether as solvent, mp 97-98°; ir (chloroform): 1655  $\text{cm}^{-1}$  (C=I-); uv (methanol): 320 nm; nmr (deuteriochloroform):  $\delta$  7.2-7.4 (pair, c, 10, Ph), 2.35 (s, 6, -CH<sub>3</sub>), 2.2-2.5 (c, 4, -CHCH<sub>2</sub>CH), 1.6 (c, 2, -CH-C-CH); ms: (70 eV); m/e Calcd. for C<sub>22</sub>H<sub>22</sub>O: 302.167, Found: 302.166.

Anal. Calcd. for C<sub>22</sub>H<sub>22</sub>O: C, 87.38; H, 7.33. Found: C, 87.20; H, 7.42.

#### 2,6-Dibenzal-cyclohexanone bis-Epoxy (5).

To a solution of 685 g (0.025 mole) of **1** in 75 ml of dioxane a mixture of 125 ml of methanol, 5 ml of water, 0.3 g of sodium hydroxide and 35 ml of 30% hydrogen peroxide was added. The reaction was kept at about 40° for two hours. An excess of water and ether was added and the solid remaining was collected and recrystallized from ethyl acetate providing 1.16 g (15%) of oxide, mp 223-225°; ir (carbon tetrachloride): 1730  $\text{cm}^{-1}$ ; uv (methanol): 271 nm, 301 nm; nmr (deuteriochloroform):  $\delta$  7.3 (s, 10, Ph), 4.1 (s, 2, -CH), 1.9-2.3 (m, 2, -CH<sub>2</sub>), 1.55, 1.65 (pair, m, 4, -CH<sub>2</sub>-C-

CH<sub>2</sub>); ms: (70 eV), m/e Calcd. for C<sub>20</sub>H<sub>16</sub>O<sub>3</sub>: 306.126, Found: 306.125.

Anal. Calcd. for C<sub>20</sub>H<sub>16</sub>O<sub>3</sub>: C, 78.41; H, 5.92. Found: C, 78.38; H, 6.09.

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