# ON THE SEARCH FOR THE MECHANISM OF PHOTOREACTIONS OF SOME HETEROCYCLIC COMPOUNDS

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## ABSTRACT

Photochemical inversion of the sequence of carbon and nitrogen atoms in five-membered heterocycles being a rather common phenomenon, the mechanism of a reaction of this type, the isomerization of some 2-alkylindazoles to the corresponding 1-alkyl-benzimidazoles has been investigated. The reaction is shown to be monomolecular and monophotonic. It starts from the lowest excited singlet state. The u.v. spectrum of an intermediate with lifetime in the order of seconds at room temperature could be determined. There is some evidence for the existence of a further short-lived precursor. Several theoretical models have been applied to speculate on the nature of the primary step.

# **1. INTRODUCTION**

In this paper we deal with photoreactions of some five-membered heterocycles. During recent years it has been shown in a number of chemical investigations that isomerizations consisting of a change in the sequence of ring-atoms seem to be most characteristic. We refer to the following examples.





Similar rearrangements also occur in benzisoxazoles<sup>5</sup>



 $R = -H, -5 - CH_3, -6 - CH_3, -7 - CH_3, -7 - OCH_3$ 

and in 2-alkyl-indazoles<sup>4</sup>



In 1-alkyl-indazoles ring opening and migration of a hydrogen atom becomes the predominant photoreaction<sup>4</sup>



The furan and isoxazole rearrangements have been shown to pass through intermediate cyclopropenyl ketones<sup>1</sup> and ketoazirines<sup>3</sup> respectively



which are converted to the final product in a second photochemical step. 496

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No intermediates have been detected so far in other reactions of this type. It has been argued that similar intermediates should occur in the photo-reactions of thiazoles<sup>2</sup>, pyrazoles and indazoles<sup>4</sup>. It is indeed not very probable for such rearrangements to occur in a concerted mechanism.

Some time ago we therefore began exploring the mechanism of 2-alkylindazole isomerizations by spectroscopic methods<sup>6</sup>. These compounds were chosen because of their especially clean reactions. Under certain conditions the chemical yield is almost 100 per cent. Furthermore we had the advantage of substantial help from Professor Schmid and co-workers in chemical problems.

## 2. SPECTROSCOPIC INVESTIGATIONS OF THE PHOTOREACTIONS OF 2-ALKYL-INDAZOLES TO 1-ALKYL-BENZIMIDAZOLES

#### 2.1. Chemical yields and quantum yields

The chemical yield of benzimidazole depends to some extent on the solvent, the temperature and the wavelength of the exciting light. Whenever isomerization occurs, the chemical yield is never less than 85 per cent at room temperature. The purest reactions are found when the wavelength of the exciting light is greater than 300 m $\mu$ . At room temperature we obtained the isomer yields given in *Table 1*.

Table 1. Chemical yield of isomerization of 2-alkylindazoles to 1-alkylbenzimidazoles. Exciting light  $\lambda \ge 300$  mµ,  $10^{-4}$  M solutions in *n*-hexane. Room temperature.

Compound	% Isomer	% Byproduct	$\Phi_{R}$
11a 2-Me-indazole	≥ 99	< 1	0.15
11b 2-t-But-indazole	≥ 99	< 1	0.045
11c 2.4-Dime-indazole	96	4	0.045
11d 2-t-But-4-me-indazole	0	100	0.006

It can be seen that 2-t-butyl-4-methylindazole does not isomerize at all, a fact that makes this compound very useful for our investigations. The nature of the byproduct has not yet been elucidated. We know, however, that it is not a secondary product, since its formation starts at the very beginning of the illumination. Neither can it originate from an impurity in our samples, because at low temperature, where the isomerization is stopped, the total amount of the reactant can be transferred to the byproduct. The quantum yield of byproduct formation at room temperature [11d] is about ten times smaller than the quantum yields for the isomerizations of [11a-c]. Figure 1 shows that the reactions can be followed very well by means of spectrophotometry.

### 2.2. Molecularity

The isomerization is an intramolecular reaction. This may be concluded from the following facts:

(a) No cross-products are found upon illumination of mixtures of two indazoles with different alkyl substitution (Schmid *et al.*<sup>4</sup>).



Figure 1. Upper half: Change of absorption spectrum upon photoisomerization of [11a]. (1) Pure 2-methylindazole; (2) Spectrum of product identical with spectrum of 1-methylbenzimidazole. Lower half: Change of absorption spectrum upon illumination of [11d]. (1) Pure educt; (2) Spectrum of products. The same spectrum is found for byproducts of [11a-c].

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(b) The reaction also proceeds in crystallized cyclohexane at  $0^{\circ}C$  with a quantum yield comparable to that in *n*-hexane which is liquid at the same temperature.

(c) The quantum yield is independent of concentration. Experiments have been made with  $10^{-3}$  and  $10^{-4}$  M solutions. If the reaction proceeds from the singlet state as will be shown in section 2.3, the probability for a bimolecular step between an excited singlet and a ground state molecule should change in this concentration range. This can be concluded from the corresponding pronounced change of excimer fluorescence of hydro-carbons<sup>7</sup>.

(d) The quantum yield does not depend on the intensity of illumination. The highest intensity used was that from a super pressure mercury lamp (Philips SP 500W) at a distance of 5 cm. The quantum flux was about  $5 \times 10^{17}$  quanta/cm<sup>2</sup> sec. The weakest intensity was about a factor of 5000 less. Thus bimolecular reactions between excited species can equally be excluded.

### 2.3. Reacting state

2-Methylindazole exhibits at 25°C in *n*-hexane a weak fluorescence  $(\Phi_F = 0.014)^8$ . Phosphorescence with a lifetime of 0.75 sec and a quantum yield  $\Phi_P = 0.003$  is measured at -80°C in outgassed triacetin glass<sup>9</sup>. A reaction from either singlet or triplet state would thus be possible. We found, however, that flushing the solution with pure oxygen, air, argon or nitrogen did not affect the quantum yield of the reaction.

In solid cyclohexane at  $-15^{\circ}$ C both the reaction and the phosphorescence could be observed. When such a solution was saturated with oxygen, the phosphorescence yield decreased by a factor of 1.5, whereas the quantum yield of the reaction remained unchanged. From this we conclude that the isomerization does not involve the triplet state.

## 2.4. Intermediates

A first indication for the presence of at least one intermediate came from the study of the pH-dependence of the isomerization of 2-methylindazole to 1-methylbenzimidazole. The quantum yield decreased from the normal value at pH = 7 to zero at pH = 4. This corresponds to a pK = 5.5 of some species, which fails to give the isomer in the protonated form. On the other hand, from the absorption and fluorescence spectra the pK values of 2methylindazole in its ground and first excited singlet state could be determined as 2.0 and about 3 respectively. The reactant can thus not be responsible for the pH dependence.

Much more direct evidence comes from spectrophotometric experiments.  $10^{-4}$  M solutions of 2-alkylindazoles were illuminated for one to several seconds by a high intensity lamp so that a large part of the compound could undergo isomerization. The subsequent time dependence of the optical density has been measured at different wavelengths. Figure 2 shows such a time dependence observed at  $\lambda = 284$  mµ as an example. It clearly proves the existence of an intermediate with a lifetime of the order of seconds.







Figure 3. Upper half: Extinction coefficients in n-hexane of: (1) 2-t-but-indazole [11b], (2) 1-t-but-benzimidazole, (3) intermediate Z. Lower half: Optical density of: (1) [11b]; (2) solution (1) after short illumination at room temperature and thermal quenching to -20°C. The spectrum is a superposition of 50% [11b], 10% isomer, 40% intermediate; (3) solution (2) after warming up to room temperature. It is a superposition of 60% [11b] and 40% isomer.

It turned out that by sudden cooling of the solutions immediately after illumination to  $-20^{\circ}$ C the intermediate could be stabilized. This allowed us to measure the whole spectrum as shown in *Figure 3*.

By comparison of these curves we could work out the spectrum of the intermediate Z. After warming up to room temperature, part of the intermediate is thermally converted to the isomer, whereas another part turns back to give the indazole. The situation with the four compounds investigated is shown in *Figure 4*.



Figure 4. First order thermal reaction constants of intermediates Z (n-hexane, room temperature).

Not much information can be obtained from the u.v. spectrum of the intermediate Z. However, a structure analogous to that of the isoxazole intermediate appears to be hardly compatible with it.

Chemical trapping of Z by a dienophile such as maleic anhydride or tetracyanoethylene failed. A diene structure thus seems not to be probable for this intermediate. We shall try to get the n.m.r. spectrum by low temperature stabilization of Z.

### 2.5. The reaction in acid solution

In aqueous sulphuric acid the reaction leads with a chemical yield of 20 per cent to the following aromatic aldehyde<sup>10</sup>. No isomerization is obtained, as mentioned before.



If 2-t-butyl-indazole is first converted to Z by short illumination in hexane, Z may be extracted by aqueous sulphuric acid giving a thermally stable compound which we tentatively write  $ZH^{\oplus}$ . In a second photochemical step with high quantum yield this can be converted to the final



Figure 5. Upper half: Absorption spectra in aqueous sulphuric acid of: (1) 2-t-butyl-4-methylindazole [11d], (2) photoproduct, (3) intermediate ZH<sup>+</sup>. Lower half: (1) Absorption spectrum of [11d] in aqueous sulphuric acid; (2) Short illumination of [11d] in hexane and extraction by aqueous sulphuric acid. The spectrum of the aqueous extract is a superposition of [11d] and ZH<sup>+</sup>; (3) solution (2) after illumination.

product of the reaction in sulphuric acid. The reaction in acid is thus a twostep photoreaction. Furthermore, these experiments indicate that the reaction path in aqueous sulphuric acid branches from that in organic solvents only at the intermediate Z.

From a structural analysis of  $ZH^{\oplus}$  we hope to get more information on Z.

# 2.6. Indications for further intermediates

After illuminating 2-alkyl-indazoles at lower temperatures it is found that the yield of Z decreases. It almost vanishes at  $-100^{\circ}$ C. So there must be a further thermally activated step between  $S_1$  of the reactant and Z. It is not impossible but not very probable that such thermal activation is involved in the direct transition from  $S_1$  to Z.

In this connection the following observation is worth mentioning: The T-T absorption spectrum of 4-methyl-2-t-butylindazole was measured<sup>11</sup> with the set-up shown in Figure  $6^{12}$  at low temperatures, where Z is not formed.



Figure 6. Experimental set-up for measuring T-T absorption spectra. Chain-dotted line: probing light beam; dashed line: exciting light beam; X<sub>1</sub> xenon high pressure lamp (Osram XBO 450W); X<sub>2</sub> xenon-mercury high pressure lamp (Hanovia 901-B1); L<sub>1</sub>-L<sub>6</sub> quartz lenses; M<sub>1</sub>, M<sub>2</sub> grating monochromators; PM photomultiplier (Philips 150 UVP); P photocell (reference signal); T<sub>1</sub>, T<sub>2</sub> tungsten lamps; F<sub>1</sub>, F<sub>2</sub> filters; S sample cell; C light chopper; A lock-in amplifier; R recorder.

The lifetime of the triplet state was obtained from the decay of the phosphorescence<sup>9</sup>. It is given in Table 2. However, by varying the frequency of the light shutter it was found that the triplet state is populated from a species, say Z' with a lifetime of  $10^{-2}$  to some  $10^{-4}$  sec, depending on the temperature.

This cannot be the singlet nor a higher triplet state of the reactant. However, a triplet state of some chemically different species (or even a singlet ground state of some high energy intermediate) could have the measured lifetime for transformation to the lowest triplet state of the reactant. In

utions of 2-t-butyl-4-methylindazole in 2-me pentane			
Decay constant in $sec^{-1}$			
of $\mathbf{Z}'$	of T		
2300			
230			
100			
	2.5		
65			
	tyl-4-methylinda pentane Decay const of Z' 2300 230 100 65		

Table 2 Decay constants of Z' and T in outgassed

preliminary e.s.r. measurements it has been possible to detect signals which, however, could not yet definitely be assigned to Z'.

If, as a working hypothesis, we identify Z' with a probable further intermediate between  $S_1$  and Z in the reaction path, we arrive at the following proposition for a possible mechanism of the photoisomerization (*Figure 7*).



Figure 7. Tentative reaction mechanism of isomerization reaction from 2-alkyl-indazole to 1-alkyl-benzimidazole.

## 3. QUANTUM CHEMICAL CONSIDERATIONS

In view of the large amount of energy which a molecule takes up from the photon it is not astonishing at all to find that in a photochemical reaction a number of chemically rather unstable intermediates are passed before a stable final product is formed. Most of these intermediates will be in their electronic ground state. Thus predicting or interpreting the course of a photochemical reaction usually will imply consecutive thermal reactions as well as the primary process. Nevertheless a theoretical understanding of the primary step is most important because it will determine to a great extent the nature of the consecutive reactions. With this aim we tried different models which may be applied to intramolécular reactions.

(a) A variety of primary steps would be compatible with orbital symmetry conservation. A decision between several possibilities such as e.g.



is not possible without quantitative arguments. Such may be deduced from explicit calculations of MO coefficients.

As an example we give in [20] the coefficients of the  $\pi$ -orbital which, according to the CNDO calculations, is the highest occupied orbital in both the lowest excited singlet and triplet state of pyrazole.



Similar coefficients were found for the corresponding isoxazole. The excited compound could thus be expected to pass by a disrotatory motion to [21].

From PPP-SCF calculations for 2-methylindazole we obtained for the highest occupied  $\pi$ -orbital in the lowest singlet state the coefficients given in [22].



This might form [19c] rather than [19a] or [19b]. Based on chemical arguments [19c] has already been proposed by Schmid *et al.*<sup>4</sup>. From this structure it is possible to obtain the isomer by further sigmatropic rearrangements.

(b) Upon excitation bond orders  $p_{\mu\nu}$  between two orbitals, one on atom A, the other on atom B, will change. As a consequence the contribution of this bond to the total energy will change by  $\Delta E_{AB}$ . If in the ground state the molecule was near to the equilibrium position, in the Franck-Condon state the bonds with positive  $\Delta E_{AB}$  will tend to become shorter and bonds with negative  $\Delta E_{AB}$  will tend to become longer. The corresponding force will be equal to the first derivative of  $\Delta E_{AB}$  with respect to the distance  $r_{AB}$  of the atoms A and B. The total force acting on an atom A will then be the vectorial sum of the forces along the directions to all other atoms.

$$\vec{K}_{\rm A} = \sum_{\rm B} \frac{\mathrm{d}\Delta E_{\rm AB}}{\mathrm{d}r_{\rm AB}} \frac{\vec{r}_{\rm AB}}{|\vec{r}_{\rm AB}|}$$

In a first approximation we put

$$\Delta E_{\mathbf{AB}} = \sum_{\mu}^{\mathbf{A}} \sum_{\nu}^{\mathbf{B}} \Delta p_{\mu\nu} \beta_{\mu\nu}$$

Neglecting the bond-bond polarizabilities we get

$$\frac{\mathrm{d}\Delta E_{AB}}{\mathrm{d} r_{AB}} = \sum_{\mu} \sum_{\nu} \sum_{\nu} \Delta p_{\mu\nu} \frac{\mathrm{d}\beta_{\mu\nu}}{\mathrm{d} r_{AB}}$$

Figure 8 shows the result of such a calculation on pyrazole. As expected, due to the excitation of a bonding electron to an antibonding orbital, the molecule gets somewhat extended in the excited state. However, the results for different excited states do not differ markedly, and the forces are too weak to make a sudden breaking of a bond very probable. One can easily estimate that the corresponding displacements of atomic equilibrium positions are in the order of 0.1 Å.



Figure 8. Forces acting on atoms in pyrazole after vertical excitation to different states. Method of calculation see text.

(c) Thermalization of vibrational and rotational degrees of freedom of an excited molecule in solution being much faster than electronic deactivation, one can try to apply similar arguments for the prediction of the primary photoreaction as usual for thermal reactions. However, the respective properties of the excited state have to be considered. As an example we<sup>13</sup> calculated the bond energies  $E_{AB}$  in different excited

As an example we<sup>13</sup> calculated the bond energies  $E_{AB}$  in different excited states of pyrazole, isoxazole and 2,4-dimethylfuran according to the energy partitioning scheme of Pople and Segal<sup>14</sup>. The results for pyrazole, which are quite similar to those for isoxazole, are given in *Figure 9*.

In all the excited states the N—N bond is the weakest, as it was in the ground state. It is thus expected to be broken most easily. For isoxazole this might lead to the intermediate found by Singh and Ullman<sup>3</sup>. For 2,4-dimethylfuran the difference of the O—C<sub>2</sub> and O—C<sub>5</sub> bond energies was not pronounced enough to allow any forecasting.

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Figure 9. Theoretical bond energies (arbitrary units) in the ground state and in some excited states of pyrazole. Method of calculation see ref. 14.

The theoretical prediction of the nature of the primary step in a photochemical reaction seems to us one of the major problems to be solved in the future.

## ACKNOWLEDGEMENTS

We would like to thank Professor Schmid and his collaborators for a number of most stimulating discussions. Messrs Bircher, Pantke and Wyrsch took several auxiliary measurements in connection with the work described in this paper. Mr Herrmann carried through the quantum chemical calculations using a programme written by Mr Kuhn. To all these collaborators of our Institute we express our thanks. Last but not least we would like to acknowledge financial support by the Schweizerischer Nationalfonds.

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