

**Mononuclear Heterocyclic Rearrangements. Part 4 (1).**  
**Synthesis and Characterization of the *E*-isomer Phenylhydrazone**  
**of 3-Benzoyl-5-phenyl-1,2,4-oxadiazole**

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3-Benzoyl-5-phenyl-1,2,4-oxadiazole (I) with phenylhydrazine in acetic acid gives the two geometrical isomers, phenylhydrazones II-Z and II-E, which have been characterized by uv-visible, ir, and nmr spectra. The possible II-E  $\rightleftharpoons$  II-Z isomerization as well as the rearrangement of II-Z and of II-E into 2,5-diphenyl-4-benzoylamino-1,2,3-triazole (III) has been pointed out.

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Mononuclear heterocyclic rearrangements of many oximes and phenylhydrazones of 3-acyl-1,2,4-oxadiazoles (2), isoxazoles (2i,3), and 1,2,5-oxadiazole (3f,4), are well documented, and largely used as a synthetic tool to obtain 1,2,5-oxadiazole and 1,2,3-triazole derivatives.

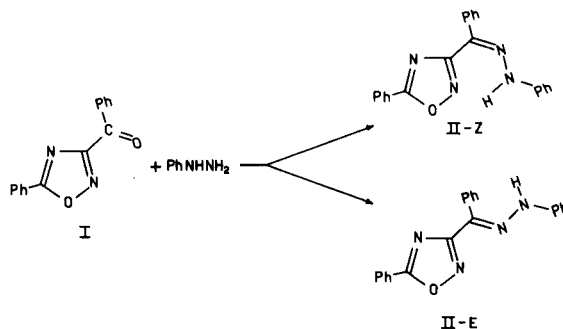
However, although the existence of geometrical isomers of phenylhydrazones of 3-acyl-1,2,5-oxadiazole has been demonstrated (5), there are no reports about the influence of the geometrical structure on the mononuclear heterocyclic rearrangements (3f).

Moreover in the case of the reaction between 3-benzoyl-5-phenyl-1,2,4-oxadiazole (I) and phenylhydrazine, only the synthesis of the *Z*-isomer phenylhydrazone II-Z has been reported (2c), and its rearrangement into 2,5-diphenyl-4-benzoylamino-1,2,3-triazole (III) has been extensively studied in dioxane/water solution (1,6).

Therefore, to extend our knowledge about the influence of the geometric structure of the phenylhydrazone II on the rate of mononuclear heterocyclic rearrangement into III, we have attempted the synthesis and the characterization of the *E*-isomer II-E. Moreover a study of the influence of the 5-membered ring and of the present substituents on the *E*  $\rightleftharpoons$  *Z* isomerization process should be possible.

#### Synthesis and Properties of II-Z and II-E.

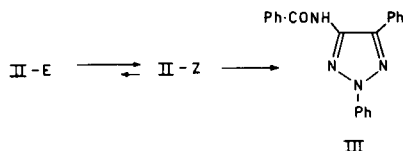
The reaction of 3-benzoyl-5-phenyl-1,2,4-oxadiazole (I) with phenylhydrazine in ethanol at room temperature, in the presence of catalytic amounts of acetic acid, gave mainly II-Z together the II-E isomer in low yield. Probably the presence of the phenylhydrazine excess affects the *Z/E* ratio through an addition-elimination mechanism (7). However, performing the reaction in acetic acid as solvent at room temperature, we obtained both isomers II-Z and II-E in 57% and 26% yields, respectively (see Experimental).



Isomer II-Z is yellow [uv-visible spectrum in dioxane:  $\lambda$  max 250 (log  $\epsilon$ , 4.55) 366 (4.22)], whereas isomer II-E is colourless [ $\lambda$  max 245 (4.43), 335 (4.31)], thus indicating a more extended conjugation in the first isomer (8). The ir spectra of II-E and II-Z, in nujol as well as in chloroform, show the presence of the phenylhydrazone NH in both isomers. Moreover, the change in the stretching frequency  $\Delta\nu$  (60-80  $\text{cm}^{-1}$ ) going from II-E to II-Z agrees with an intramolecular hydrogen bond in II-Z. The nmr spectrum of II-Z in deuteriochloroform shows the NH proton at  $\delta$  11.0, whereas in the case II-E, the NH proton resonates under a set of aromatic protons in the  $\delta$  8.10-8.40 region. The observed deshielding effect on the NH proton of II-Z, confirms the hypothesis of an intramolecular hydrogen-bonded structure in II-Z (9). In DMSO, the NH proton of II-E is shifted downfield at  $\delta$  9.45, as a consequence of solvent effect (9). The II-Z isomer, during the recording-time of the nmr spectrum in DMSO, partially rearranges into III.

The II-Z isomer is a stable solid, and it remains unchanged when refluxed for 2 hours in benzene; on the contrary, it completely rearranges into III after refluxing for 1 hour in ethanol. The II-E isomer remains unchanged, *i.e.*, it does not isomerize nor rearrange, when refluxed for 2 hours in ethanol or in benzene; after a prolonged exposure

to the light, in the solid state as well as in the solution, tlc analysis revealed the presence of some II-Z. Furthermore, we have observed that II-E (m.p. 138-140°), heated above its melting point, gives initially a mixture of II-E, II-Z, and III, and finally only III. The II-Z isomer (m.p. 137°), when heated at 150°, slowly rearranges into III. However, following the course of the reaction by tlc analysis, it is possible to detect the presence of trace-amounts of II-E. The same  $E \rightleftharpoons Z$  isomerization process has been observed when both isomers are dissolved in acetic acid at room temperature.



### EXPERIMENTAL

Melting points were determined with a Kofler hot-stage apparatus. Ir spectra were determined with a Perkin Elmer 257 instrument, uv spectra with a Zeiss PMQ II spectrophotometer, and  $^1\text{H}$  nmr (60 MHz) with a JEOL C-60H spectrometer (tetramethylsilane as internal standard). Tlc was performed on Merck aluminium sheets with silica gel 60  $F_{254}$ , using cyclohexane/ethyl acetate (10/1) as eluent. Dry column chromatography was performed on Merck silica gel deactivated with water (15%).

Reaction of 3-Benzoyl-5-phenyl-1,2,4-oxadiazole (I) with Phenylhydrazine. a) In Ethanol.

To a solution of I (1 g., 4 mmoles) in ethanol (80 ml.) containing acetic acid (0.2 ml.), phenylhydrazine (0.8 ml., 8 mmoles) was added, and the mixture was kept at room temperature in the dark. The Z-isomer (II-Z) slowly separated. After 48 hours the yellow product was filtered and washed with a minimum amount of ethanol, giving II-Z, 0.65 g., m.p. 137° (ethanol), lit. (2h) m.p. 137°, pure by tlc;  $\nu$  NH (nujol): 3230  $\text{cm}^{-1}$ ;  $\nu$  NH (chloroform): 3240  $\text{cm}^{-1}$ ; nmr (deuteriochloroform):  $\delta$  6.70-8.20 (m, 15H, 3Ph),  $\delta$  11.0 (s, 1H, NH).

The mother liquor was evaporated at reduced pressure to a small volume, diluted with water and extracted with ether. The ethereal extracts were washed repeatedly with water, dried (sodium sulfate) and evaporated. The residue was chromatographed on 150 g. of silica gel. Elution with cyclohexane/ethyl acetate (20/1) gave an additional 0.05 g. of II-Z (total yield, 0.7 g., 51%), unreacted I, and then 0.15 g. of II-E (11%), m.p. 138-140° (benzene/light petroleum);  $\nu$  NH (nujol): 3290  $\text{cm}^{-1}$ ,  $\nu$  NH (chloroform): 3320  $\text{cm}^{-1}$ ; nmr (deuteriochloroform):  $\delta$  6.80-7.70 (m, 13H, ArH),  $\delta$  8.10-8.40 (m, 3H, ortho H, NH), after a slow exchange with deuterium oxide, the two sets of signals are in the 13/2 ratio; nmr (DMSO):  $\delta$  6.70-8.40 (2m, 13 + 2 H, 3Ph),  $\delta$  9.45 (s, 1H, NH).

Anal. Calcd. for  $\text{C}_{21}\text{H}_{16}\text{ON}_4$ : C, 74.10; H, 4.74; N, 16.46. Found: C, 74.2; H, 4.9; N, 16.3.

b) In Acetic Acid.

To a solution of I (2 g., 8 mmoles) in acetic acid (25-30 ml.), phenylhydrazine (1.2 ml.; 12 mmoles) was added, and the mixture was kept at room temperature in the dark. The Z-isomer (II-Z) slowly separated. After 48 hours (tlc analysis showed the absence of the starting carbonyl compound), the yellow phenylhydrazone was filtered off and washed first with the minimum of acetic acid, and then with ethanol, yielding II-Z, 1.35 g., m.p. 137° (ethanol), pure by tlc.

The mother liquor was diluted with water to 250 ml. and the mixture was extracted with ether. The ethereal extracts were washed first with water, then with water and sodium bicarbonate to eliminate the acetic acid, and finally with water again, dried, and evaporated at reduced

pressure. The residue was rapidly chromatographed on 200 g. of silica gel using cyclohexane/ethyl acetate (20/1) as eluent, yielding an additional 0.2 g. of II-Z (total yield, 1.55 g., 57%), some fractions containing both isomer and impurities (discarded), and then fractions containing only II-E (tlc). Evaporation at reduced pressure gave a colourless residue which was taken up in light petroleum and filtered off, yielding 0.7 g. of II-E (26%), m.p. 138-140°, pure by tlc.

Fractional crystallization did not prove useful for the separation of isomers. An analytical sample of II-Z can be crystallized from ethanol or benzene/ethanol. On the contrary a colourless pure sample of II-E, without traces of the Z-isomer, can be obtained only through a rapid chromatographic separation under the conditions reported. Moreover, as to the reported procedures, we have observed that the reaction in acetic acids is the better one also because it affords cleaner samples of II-E. The time of work-up procedure and variations in experimental conditions can affect the Z/E ratio.

Heat-induced Behaviour of II-E and of II-Z.

Tubes containing 0.2 g. of II-E or II-Z were immersed in a preheated oil-bath (150°). After melting at various intervals, samples were tested by tlc.

In the case of II-E, after 15 minutes, we observed the presence of II-E, II-Z and III. At the end of the reaction (1 hour, tlc) the solid was crystallized from ethanol giving only III, m.p. 191°, lit. (2h) m.p. 191°. In the case of II-Z, after 5-10 minutes, tlc analysis shows the presence of the starting II-Z, III and trace amounts of II-E. At longer time (1 hour) the complete rearrangement of II-Z into III was observed.

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