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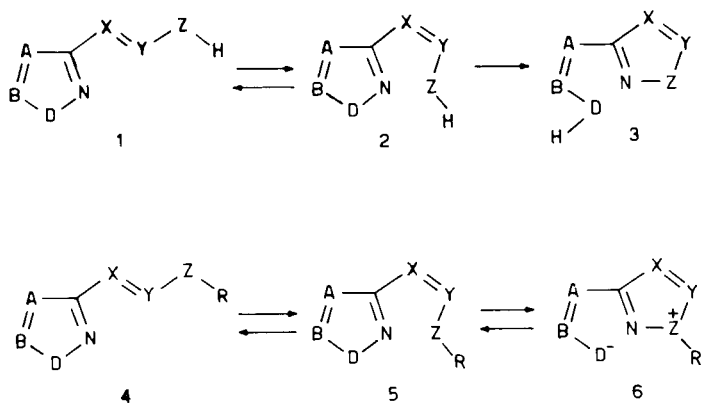
The behaviour of (*E*)- and (*Z*)-*N,N*-diphenylhydrazones and *O*-methyloximes of 3-benzoyl-5-phenyl-1,2,4-oxadiazole has been studied. When refluxed in benzene, or in dioxane-water (1:1), the (*Z*)-*N,N*-diphenylhydrazone **8Z** gave the indazole **11** or the substituted semicarbazide **12**, respectively. The *O*-methyloxime **14Z** did not give any rearrangement. A criticism of the oximation reaction of 3-benzoyl-5-phenyl-1,2,4-oxadiazole is also reported.

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In the framework of our researches concerning heterocyclic rearrangements of the type **2** → **3** [1] (mononuclear heterocyclic rearrangements; **m. h. r. s**), recently we paid attention to the influence of the geometry of the side chain sequence on the rearrangement, as well as to the system **4** ≈ **5** ≈ **6**. In this connection, we studied the reactivity of (*E*)- and (*Z*)-*N*-methyl-*N*-phenylhydrazones of 3-benzoyl-5-phenyl-1,2,4-oxadiazole [2] and of 3-benzoyl-5-phenylisoxazole [3], and we reinvestigated [4] the rearrangement of 3-acylisoxazole oximes into 1,2,5-oxadiazoles as depending on the geometry of the oxime function.

Continuing our researches on this aspect of heterocyclic rearrangements, we have now investigated the behaviour of (*E*)- and (*Z*)-*N,N*-diphenylhydrazones and *O*-methyloximes of 3-benzoyl-5-phenyl-1,2,4-oxadiazole (**7**), and a criticism of the oximation reaction of the same ketone **7** is also reported.

Scheme 1



In the reaction between 3-benzoyl-5-phenyl-1,2,4-oxadiazole (**7**) and *N,N*-diphenylhydrazine hydrochloride in acetic acid in the presence of sodium acetate, we isolated both (*Z*)- and (*E*)-*N,N*-diphenylhydrazones **8Z** and **8E** in 45% and 30% yield, respectively. This result contrasts with the behaviour [2] observed in the reaction between the ketone **7** and *N*-methyl-*N*-phenylhydrazine in acetic

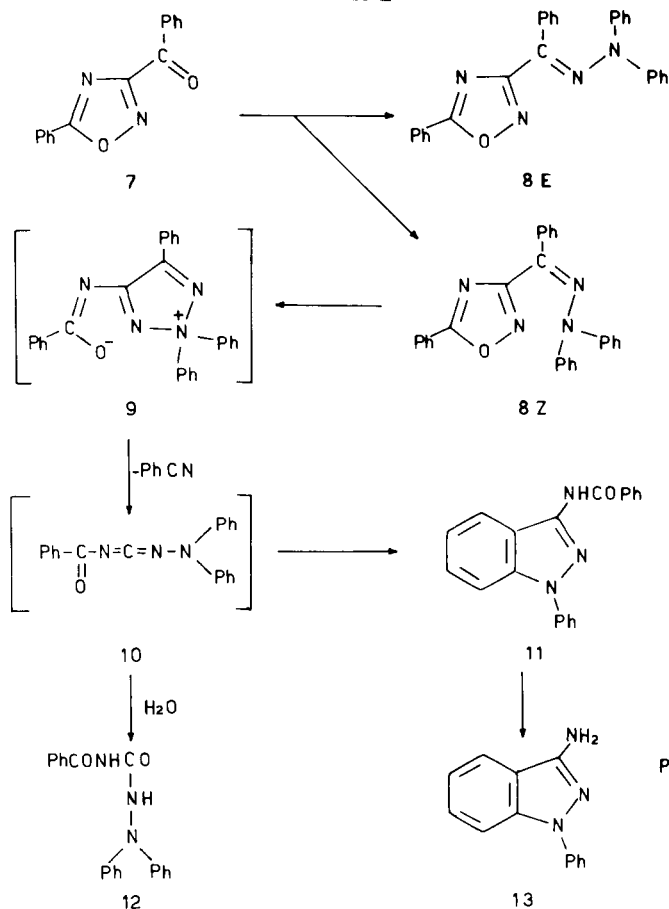
acid. In this case, in fact, only the 4-benzoylamino-2,5-diphenyl-1,2,3-triazole has been directly obtained, through a demethylation of a triazolium salt of the type **9**. When reaction between compound **7** and *N*-methyl-*N*-phenylhydrazine was performed in ethanol in the presence of *p*-nitrobenzoic acid, only isolation of the (*E*)-*N*-methyl-*N*-phenylhydrazone was claimed, as the (*Z*)-one underwent rearrangement and demethylation in the reaction medium. But a (*Z*)-*N*-methyl-*N*-phenylhydrazone has been isolated, even in low yield, for the 3-benzoyl-5-phenylisoxazole, being a ring with a lower tendency to rearrange through a **m. h. r.** [1]. The obtaining of the (*Z*)-*N,N*-diphenylhydrazone **8Z**, may be attributed to the electronic factors influencing the nucleophilic character of the *N,N*-diphenyl substituted nitrogen atom, and/or to the fact that, in this case, a *demethylation* as driving force in the rearrangement is absent.

We have also observed that the hydrazone **8Z**, when refluxed in benzene, smoothly rearranged into the benzoylaminoindazole **11** through a pathway similar to that one previously propounded [2] for the *N*-methyl-*N*-phenylhydrazone system, and reported in the Scheme. Likewise, when refluxed in dioxane-water (1:1), compound **8Z** gave the substituted semicarbazide **12**, through addition of water to the carbodiimide intermediate **10**. Structures of the rearrangement products have been assigned on the basis of analytical and spectroscopic evidences. Moreover, acid hydrolysis of compound **11** gave the aminoindazole **13** [5].

The hydrazone **8E** gave similar results, but compounds **11** and **12** were obtained in lower yield, probably due to the low *E* to *Z* isomerisation process in the *N,N*-diphenylhydrazone moiety.

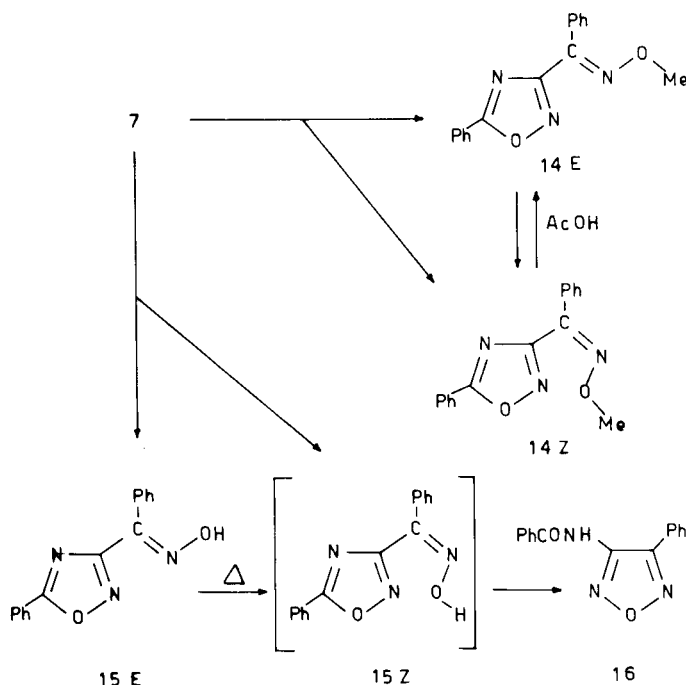
We next explored the reactivity of an *O*-methyloxime sequence. When the compound **7** was treated with *O*-methylhydroxylamine hydrochloride, gave the two foreseen *O*-methyloximes **14Z** and **14E**. These compounds did not rearrange, nor isomerize when refluxed in toluene, or dioxane-water (1:1), neither when they were melted at 120°.

Scheme 2



(mp 187°) only, and the 1,2,5-oxadiazole **16**. The 1,2,4-oxadiazole oxime remained unchanged when refluxed in ethanol in the presence of aqueous potassium hydroxide, thus suggesting an *E* configuration as in **15E** [4].

Scheme 3



The configurational stability of *O*-methyloximes is a known behaviour, indeed [6]. When refluxed in acetic acid, both isomers gave an isomerisation process, without any rearrangement. The lack of a rearrangement of the (*Z*)-*O*-methyloxime **14Z**, through a coordinated reaction of the type **5** → **6**, may be attributed to the fact that in **14Z** the sequence can assume a conformation without steric hindrance as the driving force in the rearrangement. Moreover, the possibility that the equilibrium **5** ⇌ **6** can be shifted towards the starting compound has to be considered.

The fact that both (*Z*)- and (*E*)-*O*-methyloximes were obtained prompted us to reinvestigate the reaction between the ketone **7** and hydroxylamine. It is reported in the literature [7] that oximation of compound **7** with hydroxylamine hydrochloride gave a mixture of a stable oxime (mp 186-187°, configuration not stated) and the 1,2,5-oxadiazole **16** as the rearrangement product deriving from an hypothetical "labile" intermediate oxime [7a]. It was also reported [7] that the oxime isolated rearranges into **16** at the melting point. On the reinvestigation of the oximation reaction, aiming to isolate both the (*Z*)- and (*E*)-oximes, we confirmed that, whatever experimental conditions we used, the reaction went to a mixture of an oxime isomer **15**

Considering the results obtained in the oximation reaction of 3-benzoyloxazolones [4], and the fact that both (*Z*)- and (*E*)-*O*-methyloximes were obtained, our opinion is that oximation of compound **7** with hydroxylamine should also give both the (*Z*)- and (*E*)-oximes. Owing to the high tendency [1] of the 1,2,4-oxadiazole ring to rearrange through a m. h. r., the isomer **15Z** undergoes rearrangement into **16** in the used experimental conditions and was not detected. Therefore, as anticipated [1], to the 1,2,4-oxadiazole oxime must be assigned the *E* configuration **15E**. Thermally induced rearrangement of **15E** into **16**, must be viewed as a thermally induced *E* to *Z* isomerisation process, followed by a m. h. r. reaction.

EXPERIMENTAL

Melting points were determined with a Kofler hotstage apparatus. The ir spectra (nujol) were determined with a Perkin Elmer 257 instrument, uv spectra (ethanol) with a Zeiss PMQ II spectrophotometer, ¹H nmr spectra (60 MHz) with a Varian EM 360 spectrometer (tetramethylsilane as internal standard), and mass spectra with a JEOL JMS 01-SG-2 instrument (75 eV). Dry column chromatography was performed on Riedel silica gel (0.063-0.2 mm) deactivated with water (15%). Light petroleum refers to that fraction boiling in the range of 40-60°.

3-Benzoyl-5-phenyl-1,2,4-oxadiazole (**7**) was prepared as reported [7b]. Reaction of 3-Benzoyl-5-phenyl-1,2,4-oxadiazole (**7**) with *N,N*-Diphenylhydrazine.

To a solution of compound **7** (2 g) in acetic acid (30 ml) containing sodium acetate (1.4 g), *N,N*-diphenylhydrazine hydrochloride (3.4 g) was added, and the mixture was kept at room temperature for 24 hours. After this time, water (200 ml) was added and the mixture was extracted with ether. The ethereal extracts were washed successively with water, aqueous sodium hydrogen carbonate until free of acetic acid, with water again, dried over sodium sulfate and then evaporated. Chromatography of the residue with light petroleum-ethyl acetate (100:1) gave at first the (*Z*)-*N,N*-diphenylhydrazone **8Z** [8], (1.5 g, 45%), mp 107° (from benzene-light petroleum); uv: λ max (log ϵ) 245 nm (4.49), 345 nm (4.15); nmr (deuteriochloroform): δ 6.80-8.0 (m, aromatic).

Anal. Calcd. for $C_{27}H_{20}N_4O$: C, 77.86; H, 4.84; N, 13.45. Found: C, 77.95; H, 4.90; N, 13.60.

Subsequent elution with light petroleum-ethyl acetate (50:1) gave a residue which, after crystallization from ethanol, gave the (*E*)-*N,N*-diphenylhydrazone **8E** [8] (1 g, 30%), mp 98-100° (from ethanol); uv: λ max (log ϵ) 255 nm (4.54), 342 nm (4.02); nmr (deuteriochloroform): δ 6.90-8.30 (m, aromatic).

Anal. Calcd. for $C_{27}H_{20}N_4O$: C, 77.86; H, 4.84; N, 13.45. Found: C, 77.70; H, 4.70; N, 13.50.

Rearrangement of the (*Z*)-*N,N*-Diphenylhydrazone **8Z**. a) In Benzene.

A solution of compound **8Z** (1.5 g) in anhydrous benzene (100 ml) was refluxed for 3 hours. The glc analysis (Varian 1440-10 apparatus, GE XE 60 1% column at 70°) revealed the presence of benzonitrile. After removing the solvent, the residue was chromatographed with light petroleum-ethyl acetate (10:1). After the by-products were discarded, we obtained 0.4 g (46%) of the indazole **11**, mp 198-200° (from ethanol); uv: λ max (log ϵ) 251 nm (4.36), 315 nm (4.16); ir: 3140 cm^{-1} (broad) (NH), 1650 cm^{-1} (C=O); nmr (DMSO- d_6): δ 7.20-8.30 (m, aromatic, 14H), 11.10 (s, NH, 1H); ms: *m/z* (abundance) 313 (16, M⁺), 208 (14), 105 (98), 103 (18), 77 (100), 51 (35).

Anal. Calcd. for $C_{20}H_{15}N_3O$: C, 76.66; H, 4.83; N, 13.41. Found: C, 76.50; H, 4.70; N, 13.50.

Compound **8E** in refluxing benzene gave the indazole **11** in 20% yield.

To a solution of compound **11** (0.95 g) in ethanol (100 ml), concentrated hydrochloric acid (4.5 ml) was added, and the mixture was refluxed for 30 hours. The solvent was removed and the residue was taken up with water, made alkaline with aqueous (10%) sodium hydroxide, and extracted with ether. The ethereal extracts were evaporated and the residue was chromatographed with light petroleum-ethyl acetate (2:1) giving 0.5 g of the aminoindazole **13** [5], mp 89-90° (from ethanol-water); uv: λ max (log ϵ) 258 nm (4.11), 292 nm (3.93); ir: 3160, 3270, 3420 (NH₂); nmr (DMSO- d_6): δ 6.05 (s, NH₂, 2H), 7.20-8.20 (m, aromatic, 9H).

Anal. Calcd. for $C_{15}H_{11}N_3$: C, 74.62; H, 5.30; N, 20.08. Found: C, 74.50; H, 5.40; N, 20.20.

b) In Dioxane-Water.

A solution of compound **8Z** (0.6 g) in dioxane-water (1:1) (30 ml) was refluxed for 1 hour. After cooling, the product separated was filtered off, giving 0.4 g (84%) of compound **12**, mp 230° (from ethanol); uv: λ max (log ϵ) 237 nm (4.35), 277 nm (4.08); ir: 3220-3260 cm^{-1} (NH), 1675, 1695 cm^{-1} (C=O); nmr (pyridine- d_5): δ 6.80-8.30 (m, aromatic, 15H), 11.65 and 12.25 (2 s, 2 \times NH, 2H); ms: *m/z* (abundance) 331 (19, M⁺), 210 (76), 184 (12), 183 (11), 169 (11), 168 (42), 167 (27), 105 (64), 77 (100), 51 (27).

Anal. Calcd. for $C_{20}H_{17}N_3O_2$: C, 72.49; H, 5.17; N, 12.68. Found: C, 72.60; H, 5.25; N, 12.50.

Compound **8E** under similar experimental conditions gave compound **12** in 41% yield.

Reaction of 3-Benzoyl-5-phenyl-1,2,4-oxadiazole (**7**) with *O*-Methylhydroxylamine.

A mixture of compound **7** (3 g) in ethanol (70 ml) and *O*-methylhydroxylamine hydrochloride (1.5 g) in water (15 ml) was refluxed for 2 hours. After removing the solvent, the residue was taken up with water and extracted with ether which was washed, dried and evaporated. Chromatography of the crude material with light petroleum-ethyl acetate (50:1) gave at first the (*Z*)-*O*-methyloxime **14Z** [9] (2.28 g, 68%), mp 58° (from

light petroleum); uv: λ max (log ϵ) 256 nm (4.53); nmr (deuteriochloroform): δ 4.20 (s, O-Me, 3H), 7.40-8.60 (m, aromatic, 10H).

Anal. Calcd. for $C_{16}H_{13}N_3O_2$: C, 68.80; H, 4.69; N, 15.05. Found: C, 68.70; H, 4.75; N, 15.20.

Subsequent elution gave the (*E*)-*O*-methyloxime **14E** [9] (0.9 g, 27%), mp 103° (from light petroleum); uv: λ max (log ϵ) 252 nm (4.51); nmr (deuteriochloroform): δ 4.25 (s, O-Me, 3H), 7.50-8.70 (m, aromatic, 10H).

Anal. Calcd. for $C_{16}H_{13}N_3O_2$: C, 68.80; H, 4.69; N, 15.05. Found: C, 68.85; H, 4.55; N, 14.90.

O-Methyloximes **14Z** and **14E** remained unchanged after: a) melting (2 hours) at 120° and b) refluxing (2 hours) in toluene or in dioxane-water (1:1). By refluxing (2 hours) in acetic acid, each of *O*-methyloximes gave an equilibrium mixture containing both isomers only.

Reaction of 3-Benzoyl-5-phenyl-1,2,4-oxadiazole (**7**) with Hydroxylamine.

A mixture of compound **7** (2 g) in ethanol (100 ml) and hydroxylamine hydrochloride (1.2 g) in water (10 ml) was refluxed for 3 hours. After removing the solvent, the residue was taken up with water and filtered. Chromatography of the crude material with cyclohexane-ethyl acetate (10:1) gave at first the 3-benzoylamino-4-phenyl-1,2,5-oxadiazole (**16**), (1.2 g, 57%), mp 148° (from ethanol), lit [7a] [10] mp 148°; ir: 3250 cm^{-1} (NH), 1660 cm^{-1} (C=O).

Subsequent elution gave the (*E*)-oxime **15E** (0.7 g, 33%), mp 187° (from ethanol), lit [7a,b] mp 186-187°; uv: λ max (log ϵ) 251 nm (4.44); nmr (deuteriochloroform): δ 7.40-8.40 (m, aromatic, 10H), 9.9 (s, OH, 1H); nmr (DMSO- d_6): δ 7.40-8.40 (m, aromatic, 10H), 12.30 (s, OH, 1H) [11].

The same result has been obtained by performing the oximation reaction with hydroxylamine hydrochloride: a) in ethanol at room temperature in the presence of sodium acetate; b) in ethanol in the presence of pyridine at 0-10°. Analysis (tlc) during the course of the reaction did not show the presence of other component.

The (*E*)-oxime **15E** remained unchanged after refluxing (2 hours) in ethanol in the presence of aqueous (10%) potassium hydroxide [4]. As reported [7a], the (*E*)-oxime **15E** gave compound **16** on melting.

Acknowledgements.

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- [8] Configuration has been assigned on the basis of different reactivity of the two isomers. In the region of 340 nm, the uv spectra show too small differences.
- [9] Too small differences are observed in uv and nmr spectra of the two isomers. However, the **14Z**:**14E** ratio in the reaction with *O*-methylhydroxylamine is almost the same of that observed in the reaction with hydroxylamine (**16**:**15** ratio). Furthermore, in all our chromatographic separation of mixtures containing (*E*)- and (*Z*)-oximes of 3-benzoylisoxazoles [4], the (*Z*)-isomer was the first component eluted.
- [10] S. Cusmano and M. Ruccia, *Gazz. Chim. Ital.*, **86**, 187 (1956).
- [11] The nmr spectra in deuteriochloroform and in DMSO- d_6 are in accordance with the *E* configuration for the isolated oxime. The same variation in the δ OH, going from deuteriochloroform to DMSO- d_6 has also been observed in (*E*)-oximes of 3-benzoylisoxazoles [4].