Steric Factors in Heterocyclic Rearrangements. *N*-Methyl-*N*-phenylhydrazones of 3-Benzoyl-5-phenyl-1,2,4-oxadiazole

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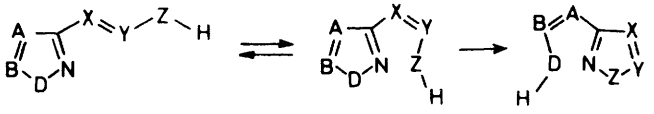
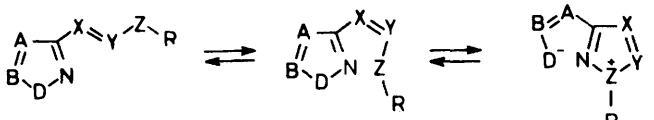
In acetic acid at room temperature, the (*E*)- and (*Z*)-*N*-methyl-*N*-phenylhydrazones of 3-benzoyl-5-phenyl-1,2,4-oxadiazole rearranged into 4-benzoylamino-2,5-diphenyl-1,2,3-triazole *via* demethylation of an intermediate triazolium salt. When refluxed in benzene, the (*E*)-*N*-methyl-*N*-phenylhydrazone (8*E*) gave 3-benzoylamino-1-methylindazole (17) through prior isomerisation to the unisolated *Z*-isomer (8*Z*) and thence *via* a carbodi-imide intermediate derived from cleavage of the ring O–N bond.

THE general scheme for mononuclear heterocyclic rearrangements of the type (2) ⟶ (3) [1] is characterized by having the side chain *cis* to the initial ring, and by the presence of a labile hydrogen atom attached to the atom Z in the original side chain. A pure rearrangement reaction, with or without base catalysis, involves formation of a Z–N bond and breaking of the D–N bond.

Continuing our research in this field,[2-4] we became interested in how geometric factors in the side chain, *e.g.* the (1) ⇄ (2) isomerisation, affect the occurrence of rearrangements. Moreover, it was of interest to study the influence of a Z–R group in a reaction of the type (5) ⇄ (6), as well as in the isomerisation (4) ⇄ (5). In this connection we looked at the behaviour of (*E*)- and (*Z*)-*N*-methyl-*N*-phenylhydrazones of 3-benzoyl-5-phenyl-1,2,4-oxadiazole (7).



(1) (2) (3)



(4) (5) (6)

SCHEME 1

When we treated compound (7) with *N*-methyl-*N*-phenylhydrazine in acetic acid at room temperature, we did not obtain the hydrazone (8*E*) or (8*Z*); the reaction gave directly 4-benzoylamino-2,5-diphenyl-1,2,3-triazole (10) in quantitative yield. On the other hand, we have reported [3] that the reaction of compound (7) with phenylhydrazine in acetic acid at room temperature gave both (13*E*) and (13*Z*), in 26 and 57% yield, respectively, without even a trace of the triazole (10).

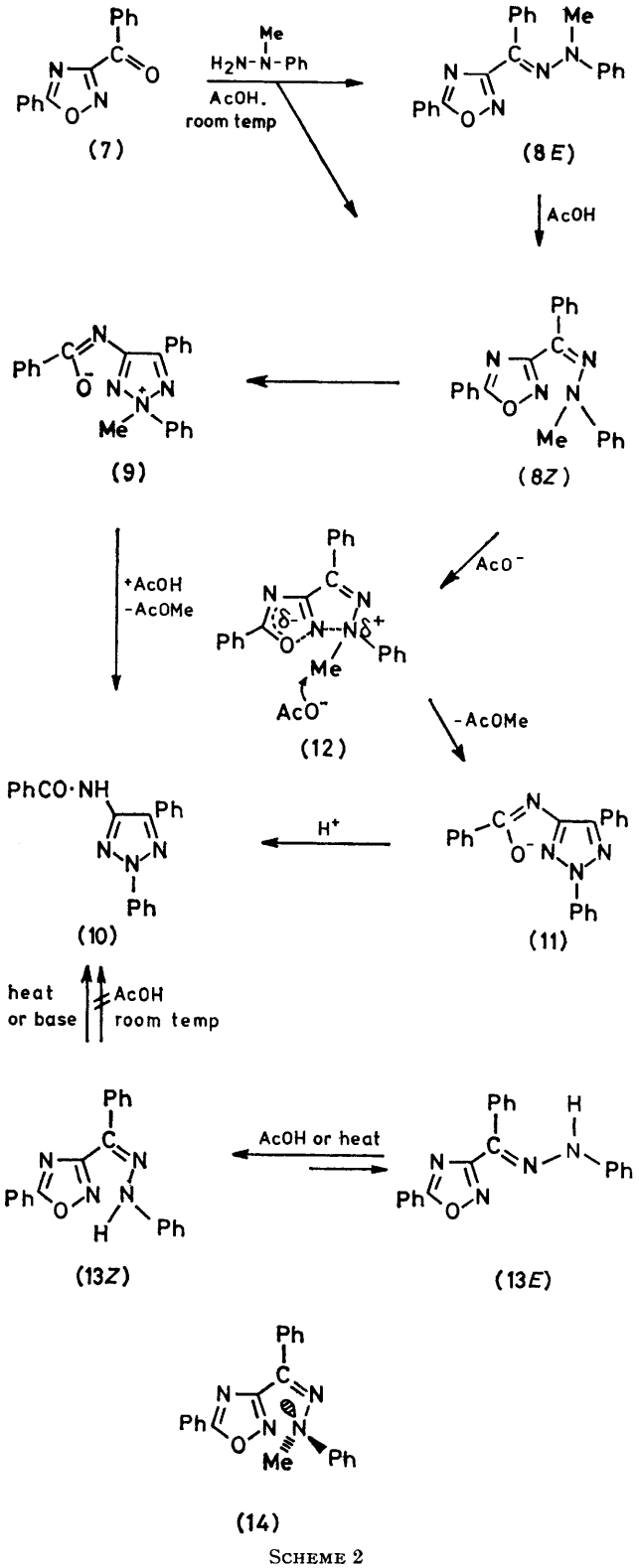
The direct formation of the triazole (10) in the above reaction may be interpreted as proceeding from the (*Z*)-*N*-methyl-*N*-phenylhydrazone (8*Z*), through the triazolium salt (9), demethylation [5] taking place by action of acetate anion (or acetic acid), or concertedly with rearrangement [see (12)].

When we treated compound (7) with *N*-methyl-*N*-phenylhydrazine in ethanol in the presence of *p*-nitrobenzoic acid, we obtained the triazole (10), methyl *p*-nitrobenzoate, and the (*E*)-*N*-methyl-*N*-phenylhydrazone (8*E*). The formation of the methyl ester accounts for the demethylation reaction, while the triazole (10) arises from the unisolated (*Z*)-hydrazone (8*Z*). As to the reaction of (7) with *N*-methyl-*N*-phenylhydrazine in acetic acid, we suggest an initial formation of both (8*E*) and (8*Z*). While (8*Z*) rearranges into (10) as it is formed, (8*E*) isomerises [6] to (8*Z*), the overall process being thus shifted towards (10). In ethanol, and in the presence of *p*-nitrobenzoic acid, a lower isomerisation rate would be expected.

Since the corresponding unsubstituted phenylhydrazone (13*Z*) does not rearrange into (10) in acetic acid, the behaviour of the *N*-methyl-substituted sequence in (8*Z*) allows us to consider the methyl-phenyl-substituted nitrogen atom as having a markedly nucleophilic character in the reaction involving attack on the ring nitrogen atom. This observation, although in part attributable to the inductive effect of the methyl group, may be due also to steric and/or electronic factors such as (i) twisting of the –N(Me)Ph group out of the plane of the C=N system [see (14)], so minimizing extended conjugation of the substituted nitrogen lone-pair; [7] (ii) forced rotation around the N–N bond of the phenylhydrazone moiety probably favouring interaction in the new N–N bond formation; (iii) hydrogen bonding in (13*Z*) [3] but not in (8*Z*), resulting in different stabilities of the two starting systems *vis-à-vis* the transition state of the rearrangement. On the other hand, the effect evidenced here recalls the '*ortho*-tertiary-amino effect' observed in other reactions.[8]

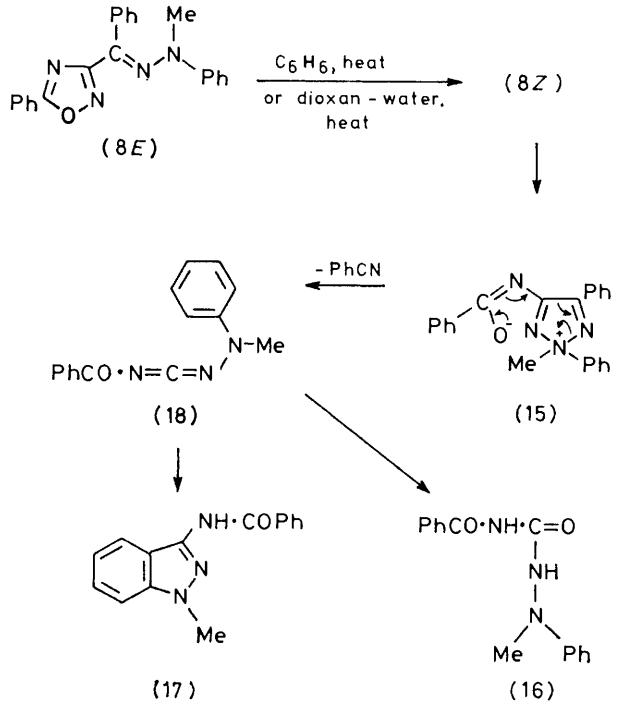
Different products were obtained from the hydrazone (8*E*) in the absence of acetic acid. When refluxed in benzene, (8*E*) gave benzonitrile and 3-benzoylamino-1-methylindazole (17). This reaction can be explained in terms of Scheme 3, involving isomerisation of (8*E*) to the (undetected) (8*Z*). Support for this mechanism is provided by the observation that refluxing (8*E*) in dioxan–water (1 : 1) gave, besides benzonitrile, the substituted semicarbazide (16), as a result of nucleophilic attack of H_2O at the carbodi-imide carbon atom of (18).

Since the (*E*)- and (*Z*)-phenylhydrazones (13*E*) and (13*Z*) are unchanged [3] when refluxed in benzene, it is



SCHEME 2

evident that the *N*-methyl-*N*-phenylhydrazone sequence behaves differently in isomerisation as well as in rearrangement. Moreover, in this case also the (*Z*)-*N*-methyl-*N*-phenylhydrazone (8*Z*) exhibits a marked reactivity in attack on the ring nitrogen atom. However, in the absence of a demethylating agent, preventing access to the 1,2,3-triazole, the rearrangement proceeds through cleavage of the triazole moiety itself.



SCHEME 3

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. I.r. spectra (Nujol mulls) were determined with a Perkin-Elmer 257 instrument, ^{1}H n.m.r. spectra (60 MHz) with a Varian EM 360 spectrometer (tetramethylsilane as internal standard), and mass spectra with a JEOL JMS-01 instrument (75 eV). Chromatography on dry columns was performed on Merck silica gel deactivated with water (15%).

Reaction of 3-*Benzoyl*-5-*phenyl*-1,2,4-*oxadiazole* (7) *with* N-*Methyl*-N-*phenylhydrazine*.—(a) *In acetic acid*. To a solution of the oxadiazole (7) [9] (1 g) in acetic acid (10 ml), *N*-methyl-*N*-phenylhydrazine (0.7 ml) was added, and the mixture was kept at room temperature. After 24 h addition of a little water and filtration gave a quantitative yield of 4-benzoylamino-2,5-diphenyl-1,2,3-triazole (10), m.p. 191 °C (from ethanol).[2a]

(b) *In ethanol in the presence of* p-*nitrobenzoic acid*. To a solution of the oxadiazole (7) (2.5 g) in absolute ethanol (150 ml) containing *p*-nitrobenzoic acid (1.6 g), *N*-methyl-*N*-phenylhydrazine (1.6 ml) was added, and the mixture was kept at room temperature for 60 h. The solution was concentrated at reduced pressure, and the solid separated and was filtered off giving the triazole (10) (1.6 g). The mother liquor was concentrated again and diluted with water, and the solid was filtered off and chromatographed on 300 g of silica gel. Elution with cyclohexane–ethyl acetate (50 : 1) gave first *methyl* p-*nitrobenzoate* (0.45 g), m.p. 96 °C (from light petroleum), and then the (E)-N-*methyl*-N-*phenyl*-

hydrazone (8*E*) (0.75 g), m.p. 94—96 °C (decomp.) (from benzene–light petroleum with freezing) (Found: C, 74.4; H, 5.0; N, 15.9. $C_{22}H_{18}N_4O$ requires C, 74.55; H, 5.1; N, 15.8%); $\lambda_{max.}$ (ethanol) 250 (log ε 4.49) and 342 nm (4.07); δ($CDCl_3$) 3.10 (3 H, s, NMe), 7.0—7.80 (13 H, m, ArH), and 8.20—8.50 (2 H, m, *ortho*-H of 5-Ph). Subsequent elution with cyclohexane–ethyl acetate (10 : 1) gave more of (10) (0.3 g). In acetic acid, compound (8*E*) gave (10) in quantitative yield.

Isomerisation and Rearrangement of (E)-N-*Methyl*-N-*phenylhydrazone* (8*E*).—(a) *In refluxing benzene.* A solution of (8*E*) (0.5 g) in benzene (20 ml) was refluxed for 2 h. G.l.c. analysis revealed the presence of benzonitrile (Varian 1440–10 apparatus; GE XE 60 1% column at 70 °C). Removal of the solvent left a residue, which was chromatographed. Elution with cyclohexane–ethyl acetate (10 : 1) gave 3-*benzoylamino*-1-*methylindazole* (17) (0.25 g, 70%), m.p. 188—190 °C (from ethanol) (Found: C, 71.7; H, 5.0; N, 16.5. $C_{15}H_{13}N_3O$ requires C, 71.7; H, 5.2; N, 16.7%); $\nu_{max.}$ 3 230 (NH) and 1 645 cm^{-1} (C=O); δ[$(CD_3)_2SO$] 4.05 (3 H, s, NMe), 7.05—8.30 (9 H, m, ArH), and 10.90 (1 H, s, NH); *m/z* 251 (M^+). A similar rearrangement, but in lower yield, takes place on heating (8*E*) at its m.p. Benzoylation of 3-amino-1-methylindazole [20] gave (17).

(b) *In refluxing dioxan–water.* On refluxing (2 h) in dioxan–water (1 : 1), compound (8*E*) gave a quantitative yield of 4-*benzoyl*-1-*methyl*-1-*phenylsemicarbazide* (16), m.p. 218 °C (from ethanol) (Found: C, 67.0; H, 5.5; N, 15.7. $C_{15}H_{15}N_3O_2$ requires C, 66.9; H, 5.6; N, 15.6%); $\nu_{max.}$ 3 280, 3 220, and 3 130 (NH), and 1 650—1 670 cm^{-1} (C=O); δ[$(CD_3)_2SO$] 3.20 (3 H, s, NMe), 6.70—8.30 (10 H, m, 2 Ph), and 10.35 and 11.0 (2 H, 2 s, 2 NH); *m/z* 269 (M^+). The reaction of benzoyl isocyanate [10] with *N*-methyl-*N*-phenylhydrazine in anhydrous benzene also gave (16).

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REFERENCES

[1] A. J. Boulton, A. R. Katritzky, and A. M. Hamid, *J. Chem. Soc.* (*C*), 1967, 2005.

[2] (*a*) M. Ruccia and D. Spinelli, *Gazz. Chim. Ital.*, 1959, **89**, 1654; (*b*) M. Ruccia and N. Vivona, *Ann. Chim.* (*Rome*), 1967, **57**, 680; (*c*) *Chem. Commun.*, 1970, 866; (*d*) M. Ruccia, N. Vivona, and G. Cusmano, *J. Heterocycl. Chem.*, 1971, **8**, 137; (*e*) *Tetrahedron Lett.*, 1972, 4959; (*f*) *Tetrahedron*, 1974, **30**, 3859; (*g*) *J. Chem. Soc., Chem. Commun.*, 1974, 358; (*h*) N. Vivona, G. Cusmano, M. Ruccia, and D. Spinelli, *J. Heterocycl. Chem.*, 1975, **12**, 985; (*i*) N. Vivona, M. Ruccia, G. Cusmano, M. L. Marino, and D. Spinelli, *J. Heterocycl. Chem.*, 1975, **12**, 1327; (*j*) D. Spinelli, A. Corrao, N. Vivona, M. Ruccia, and G. Cusmano, *J. Heterocycl. Chem.*, 1976, **13**, 357; (*k*) M. Ruccia, N. Vivona, G. Cusmano, and G. Macaluso, *J. Chem. Soc., Perkin Trans. 1*, 1977, 589; (*l*) N. Vivona, G. Cusmano, and G. Macaluso, *J. Chem. Soc., Perkin Trans. 1*, 1977, 1616; (*m*) D. Spinelli, V. Frenna, A. Corrao, and N. Vivona, *J. Chem. Soc., Perkin Trans. 2*, 1978, 19; (*n*) D. Spinelli, V. Frenna, A. Corrao, N. Vivona, and M. Ruccia, *J. Heterocycl. Chem.*, 1979, **16**, 359; (*o*) N. Vivona, G. Cusmano, G. Macaluso, V. Frenna, and M. Ruccia, *J. Heterocycl. Chem.*, 1979, **16**, 783.

[3] N. Vivona, M. Ruccia, V. Frenna, and D. Spinelli, *J. Heterocycl. Chem.*, 1980, **17**, 401.

[4] V. Frenna, N. Vivona, D. Spinelli, and G. Consiglio, *J. Heterocycl. Chem.*, 1980, **17**, 861.

[5] (*a*) W. Sucrow and M. Slopianka, *Chem. Ber.*, 1978, **111**, 780; (*b*) N. R. El-Rayyes and F. H. Al-Hajjar, *J. Heterocycl. Chem.*, 1977, **14**, 367.

[6] (*a*) C. I. S. Stassinopoulou, C. Zioudrou, and G. J. Karabatsos, *Tetrahedron Lett.*, 1972, 3671; (*b*) H. O. Kalinowski, H. Kessler, D. Liebfritz, and A. Pfeffer, *Chem. Ber.*, 1973, **106**, 1023.

[7] (*a*) G. J. Karabatsos and K. L. Krumel, *Tetrahedron*, 1967, **23**, 1097; (*b*) Y. Shvo and A. Nahlieli, *Tetrahedron Lett.*, 1970, 4273; (*c*) M. T. McCormack and A. F. Hegarty, *J. Chem. Soc., Perkin Trans. 2*, 1976, 1701.

[8] D. W. S. Latham, O. Meth-Cohn, and H. Suschitzky, *J. Chem. Soc., Perkin Trans. 1*, 1977, 478; and references therein.

[9] S. Cusmano and M. Ruccia, *Gazz. Chim. Ital.*, 1955, **85**, 1686.

[10] A. Etienne, B. Bonte, and B. Druet, *Bull. Soc. Chim. Fr.*, 1972, 251.