Mononuclear Heterocyclic Rearrangements. Part 10.[1] Rearrangements in the 1,2,5-Oxadiazole Series

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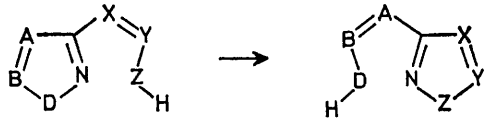
By studying the chemical behaviour of *N*-(4-methyl-1,2,5-oxadiazol-3-yl)-*N'*-phenylurea and of *N*-(4-methyl- or phenyl-1,2,5-oxadiazol-3-yl)-*N'*-arylformamidines in mononuclear heterocyclic rearrangements and comparing these results with those already obtained in the 1,2,4-oxadiazole and isoxazole series, relative tendencies towards mononuclear heterocyclic rearrangement have been estimated; *viz.* 1,2,4-oxadiazole > isoxazole > 1,2,5-oxadiazole.

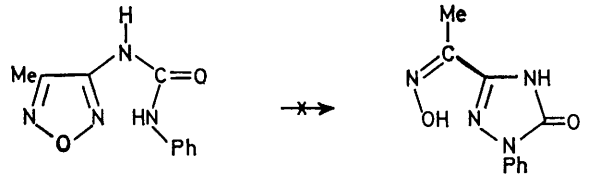
In previous papers [2] we have reported studies on mononuclear heterocyclic rearrangements of the general type (1) ⟶ (2).[3] Although a large number of ABD and XYZ combinations [3,4] can be envisaged, it was found that rearrangements of this type occur only with 1,2,4-oxadiazoles, isoxazoles, and 1,2,5-oxadiazoles (1; D = O), containing a suitable XYZ side-chain. The three heterocyclic systems, however, show differences in rate and in conditions for rearrangement. We planned to investigate the dependence of reactivity on the structure of both the starting ring system and the side chain, and began by comparing the behaviour of the three heterocycles carrying the same side-chain. We now report a



(1) (2)

study of the 1,2,5-oxadiazole system (1; ABD = CNO) carrying, as XYZ, the NCN sequence of a ureido-group (–NH–CO–NHPh) or a formamidino-group (–N=CH–NHAr) and a comparison of the results with those for the corresponding 1,2,4-oxadiazoles and isoxazoles.

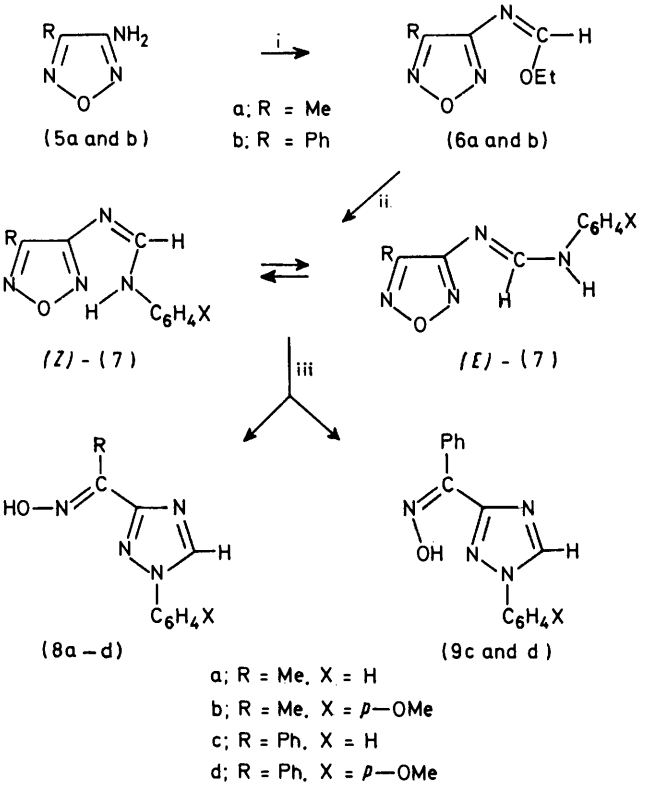
Attempts to rearrange the ureido-derivative (3) to (4) were not successful. Unsuccessful attempts to rearrange *N*-(5-methylisoxazol-3-yl)-*N'*-phenylurea have



(3) (4)

also been reported.[3] In contrast, *N*-(5-substituted 1,2,-4-oxadiazol-3-yl)-*N'*-phenylureas rearrange to 3-acylamino-1,2,4-triazolin-5-ones in the presence of base.[2e]

With the more nucleophilic formamidino side chain, both 1,2,4-oxadiazole [2d] (1; ABD = NCO) and isoxazole [5] (1; ABD = CCO) rearrange to 1,2,4-triazole derivatives (2; XYZ = NCN). We therefore investigated the behaviour of the arylformamidines (7), prepared as outlined in the Scheme.



(5a and b) (6a and b) (Z)-(7) (E)-(7) (8a–d) (9c and d)

a; R = Me
b; R = Ph

a; R = Me, X = H
b; R = Me, X = *p*—OMe
c; R = Ph, X = H
d; R = Ph, X = *p*—OMe

SCHEME Reagents: i, $HC(OEt)_3$; ii, $PhNH_2$ or *p*-$MeO{\cdot}C_6H_4{\cdot}NH_2$; iii, $KOBu^t$–$Me_2N{\cdot}CHO$

Experimental conditions (such as heating, treatment with sodium hydroxide at room temperature, or refluxing with sodium ethoxide in ethanol) which proved suitable to rearrange 1,2,4-oxadiazole or isoxazole derivatives, failed in this case. To obtain rearrangement it was

[1] The papers quoted in references 2*g*, 2*h*, and 2*i* should be considered as Parts 7, 8, and 9, respectively, of this series.

[2] (*a*) M. Ruccia and D. Spinelli, *Gazzetta*, 1959, **89**, 1654; (*b*) M. Ruccia and N. Vivona, *Ann. Chim.* (*Italy*), 1967, **57**, 680; (*c*) *Chem. Comm.*, 1970, 866; (*d*) M. Ruccia, N. Vivona, and G. Cusmano, *J. Heterocyclic Chem.*, 1971, **8**, 137; (*e*) *Tetrahedron Letters*, 1972, 4859; (*f*) *Tetrahedron*, 1974, **30**, 3859; (*g*) *J.C.S. Chem. Comm.*, 1974, 358; (*h*) N. Vivona, G. Cusmano, M. Ruccia, and D. Spinelli, *J. Heterocyclic Chem.*, 1975, **12**, 985; (*i*) N. Vivona, M. Ruccia, G. Cusmano, M. L. Marino, and D. Spinelli, *ibid.*, p. 1327.

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

[4] A. J. Boulton, 'Lectures in Heterocyclic Chemistry,' 1973, vol. II, S–45; Fourth International Congress of Heterocyclic Chemistry, July 1973, Utah, U.S.A., and references cited therein.

[5] H. Kano and E. Yamazaki, *Tetrahedron*, 1964, **20**, 159.

necessary to employ potassium t-butoxide in dimethylformamide, at 130 °C for 6 h, which gave the rearrangement products in 60—80% yield. Rearrangement of (7a and b) afforded only the *syn*-methyl isomers (8a) [6,*] and (8b), whereas rearrangements of (7c and d) gave mixtures (1 : 1 ratio) of *E*- and *Z*-oximes [(8c) + (9c)] [7] and [(8d) + (9d)], respectively.

The results point to a decreasing reactivity in the transformation (1) ⟶ (2) on going from 1,2,4-oxadiazole to isoxazole to 1,2,5-oxadiazole. The controlling factor could well be the differences in electronic structure of ring, with respect to the nature of the O–N bond,[8] which is cleaved in the rate-determining step,[9] and also with regard to the ability of the leaving ABO sequence to accommodate the incipient negative charge which appears in the transition state.[9] As to the side-chain, the difference in behaviour of the ureido and formamidino sequences agrees with their nucleophilic reactivities under the reaction conditions.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. I.r. spectra (Nujol mulls) were determined with a Perkin-Elmer Infracord 137 instrument, u.v. spectra (solutions in 95% ethanol) with a Beckman DB (with recorder) spectrophotometer, and ^{1}H n.m.r. spectra (60 MHz) with a JEOL C-60H spectrometer (tetramethylsilane as internal standard). Chromatography was performed with Merck silica gel, deactivated with water (15%).

N-(4-*Methyl*-1,2,5-*oxadiazol*-3-*yl*)-N′-*phenylurea* (3).— A mixture of 3-amino-4-methyl-1,2,5-oxadiazole (5a) [10] (4 g) and phenyl isocyanate (6 ml) was heated in an oil-bath at 100 °C, and kept for ½ h at this temperature. After cooling, the product was worked up with anhydrous benzene and filtered off. Crystallization from ethanol gave the urea (3)[11] (4.5 g), m.p. 215° (Found: C, 55.15; H, 4.5; N, 25.5. Calc. for $C_{10}H_{10}N_4O_2$: C, 55.05; H, 4.6; N, 25.7%); δ [$(CD_3)_2SO$] 2.34 (3 H, s, CH_3), 6.80—7.65 (5 H, m, Ph), and 8.95 and 9.25 (2 H, 2s, NH).

The urea (3) was unchanged after (*a*) heating at its m.p. for ½ h; (*b*) refluxing for 5 h with aqueous 10% potassium hydroxide in ethanol; (*c*) keeping with potassium t-butoxide in dimethylformamide solution at room temperature for many days. Heating with potassium t-butoxide in dimethylformamide afforded decomposition products only.

3-*Ethoxymethyleneamino*-4-*methyl*-1,2,5-*oxadiazole* (6a).— A mixture of the amine (5a) (15 g), ethyl orthoformate (80 ml), and a few drops of acetic acid was refluxed for 50 h, with removal of ethanol formed in the reaction. Removal of the excess of ethyl orthoformate left an oily residue, which on fractional distillation under reduced pressure yielded the *imine* (6a) (12 g), b.p. 125—130° at 20 mmHg (Found: C, 46.5; H, 5.9; N, 27.15. $C_6H_9N_3O_2$ requires C, 46.45; H, 5.85; N, 27.1%); δ ($CDCl_3$) 1.39 (3 H, t, O·CH_2·CH_3), 2.28 (3 H, s, CH_3), 4.38 (2 H, q, O·CH_2·CH_3), and 8.26 (1 H, s, CH).

3-*Ethoxymethyleneamino*-4-*phenyl*-1,2,5-*oxadiazole* (6b).— This compound was prepared similarly from the amine (5b).[12] Removal of the excess of ethyl orthoformate and addition of light petroleum to the oily residue, after cooling in an ice-bath, yielded the *imine* (6b) (70%), m.p. 43° (from light petroleum) (Found: C, 60.7; H, 5.0; N, 19.45. $C_{11}H_{11}N_3O_2$ requires C, 60.8; H, 5.1; N, 19.35%); δ ($CDCl_3$) 1.41 (3 H, t, O·CH_2·CH_3), 4.45 (2 H, q, O·CH_2·CH_3), 7.30—8.25 (5 H, m, Ph), and 8.32 (1 H, s, CH).

General Method for the Preparation of N-(4-*Substituted* 1,2,-5-*oxadiazol*-3-*yl*)-N′-*arylformamidines* (7a—d).—A solution of equimolar amounts of the imine (6) (0.02 mol) and the amino compound (aniline or *p*- methoxyaniline), in dry tetrahydrofuran (20 ml), was set aside at room temperature for 4—5 days. When t.l.c. showed the absence of starting materials, the mixture was evaporated to dryness under reduced pressure. The minimum of anhydrous benzene was added to the residue, and after solidification the product was filtered off. Crystallization from benzene–petroleum (1 : 1) gave the arylformamidine (7) (80%). The same compounds were also obtained by keeping equimolar amounts of reactants (0.01 mol) in an oil bath at 100—110 °C for 2 h. After cooling, the mixture was taken up in anhydrous benzene and the product filtered off as above; yield 70%. Analytical and physical data are reported in Tables 1 and 2.

The arylformamidines (7) were unchanged after heating at 140 °C for 3—4 h. Refluxing for 2—3 h with sodium ethoxide in ethanol, or treatment with aqueous potassium hydroxide in ethanol, resulted mainly in hydrolysis.

The existence of geometric and/or tautomeric forms of the arylformamidines (7) would be expected. Work is in progress on the possibility of tautomerism (using $Ph^{15}NH_2$). N.m.r. spectra (Table 2) showed the presence of *Z*- and *E*-forms, identified on the basis of the CH,NH coupling constant (13 Hz for the *Z*-system).[13] The low-field position of the NH signal of the *Z*-form, and its independence of concentration, is consistent with a hydrogen-bonded structure. The lower field position of the CH signal of the *E*-form is consistent with deshielding by the sp^2 ring nitrogen atom.

General Method for the Rearrangement of Arylformamidines (7a—d) *to the Oximes of* 3-*Acyl*-1,2,4-*triazoles* (8a—d) *and* (9c *and* d).—A mixture of equimolar amounts of the amidine (7) (0.015 mol) and potassium t-butoxide, in dimethylformamide (20 ml) was heated for 6 h at 120—130 °C. After cooling, water (150 ml) was added and the mixture was neutralized with acetic acid. The product after purification was obtained in 60—80% yield. The mixtures of oximes obtained from (7c and d) (6 g) were chromatographed on a dry column of deactivated silica gel (300 g). Elution with cyclohexane–ethyl acetate (2 : 1) gave the lower melting Z-*oxime* (9c or d). Elution with ethyl acetate then gave the higher melting E-*oxime* (8c or d). Samples for analysis were crystallized from suitable solvents (see Table 1). Analytical and physical data are reported in Tables 1 and 2.

As reported for (9c),[7] (9d) undergoes the Beckmann rearrangement with polyphosphoric acid. The E-*oximes* (8a—d) also underwent the Beckmann rearrangement with phosphorus pentachloride in chloroform (see later).

* Ref. 6 does not report the configuration for (8a).

[6] N. N. Vereshchagina and I. Ya. Postovskii, *Nauch. Doklady Vysshei Shkoly, Khim. i khim Tekhnol.*, 1959, 341 (*Chem. Abs.*, 1960, **54**, 510).

[7] E. J. Browne and J. B. Polya, *J. Chem. Soc.* (*C*), 1968, 824.

[8] (*a*) W. Adam and A. Grimison, *Theor. Chim. Acta*, 1967, **7**, 342; (*b*) M. Kamiya, *Bull. Chem. Soc. Japan*, 1970, **43**, 3344.

[9] D. Spinelli, A. Corrao, V. Frenna, N. Vivona, M. Ruccia, and G. Cusmano, *J. Heterocyclic Chem.*, 1976, **13**, 357.

[10] S. Cusmano and T. Tiberio, *Gazzetta*, 1951, **81**, 106.

[11] G. Westphal and R. Schmidt, *J. prakt. Chem.*, 1973, **315**, 791.

[12] F. Angelico and S. Cusmano, *Gazzetta*, 1936, **66**, 3.

[13] S. Polanc, B. Verček, B. Stanovnik, and M. Tišler, *J. Heterocyclic Chem.*, 1974, **11**, 103, and references cited therein.

N.m.r. spectra of the oximes (Table 2) showed OH signals at low field for all compounds in $(CD_3)_2SO$ solution. However in $CDCl_3$ (when solubility allowed) the OH signals occurred at low field for (9c and d), but at higher field for (8a and b). This fact can be explained as a result of intramolecular hydrogen bonding with N-2 of the ring in the *Z*-oximes (9) and of a deshielding solvent effect in the *E*-oximes (8).

Beckmann Rearrangement of the E-*Oximes* (8a—d) *with Phosphorus Pentachloride*.—The oxime (0.01 mol) in dry chloroform (60 ml) was cooled in an ice-bath, and phosphorus pentachloride (0.015 mol) was added. The mixture was set aside at room temperature for 2 days and then the solvent was allowed to evaporate off spontaneously. The residue was triturated with the minimum of ethanol and then water was added. The mixture was made alkaline (pH 8—9) with ammonium hydroxide and then extracted (3 times) with chloroform. The combined extracts were dried and evaporated at reduced pressure; the residue was crystallized from ethanol, yielding (20%) (a) 3-acetamido-1-phenyl-1,2,4-triazole, m.p. 168° (lit.,[2d] 168°); (b) 3-*amino*-1-p-*methoxyphenyl*-1,2,4-*triazole*, m.p. 185° (Found: C, 56.7; H, 5.25; N, 29.3. $C_9H_{10}N_4O$ requires C, 56.85; H, 5.3; N, 29.45%), $\nu_{max.}$ 3 448, 3 289, 3 175, and 3 085 cm^{-1}, δ [$(CD_3)_2SO$] 3.76 (3 H, s, OMe), 5.57 (2 H, s, NH_2), 6.85—7.80 (4 H, m, ArH), and 8.67 (1 H, s, CH); (c) 3-benzamido 1-phenyl-1,2,4-triazole, m.p. 172° (lit.,[2d] 172°); or (d) 3-*benzamido*-1-p-*methoxyphenyl*-1,2,4-*triazole*, m.p. 182—183° (Found: C, 65.5; H, 4.85; N, 19.1. $C_{16}H_{14}N_4O_2$ requires C, 65.3; H, 4.8; N, 19.05%), $\nu_{max.}$ 3 185, 3 096, and 1 692 cm^{-1}, $\lambda_{max.}$ 262 (log ε 4.34) and 236—229 nm (plateau, log ε 4.22), δ [$(CD_3)_2SO$] 3.80 (3 H, s, OMe), 7.0—8.20 (9 H, m, ArH), 9.08 (1 H, s, CH), and 10.92 (1 H, s, NH).

Beckmann Rearrangement of the Z-*Oxime* (9d) *with Polyphosphoric Acid*.—This rearrangement was performed as described by Browne and Polya[7] yielding 1-p-*methoxyphenyl*-3-*phenylcarbamoyl*-1,2,4-*triazole*, m.p. 180—181° (from ethanol) (Found: C, 65.25; H, 4.75; N, 18.9. $C_{16}H_{14}N_4O_2$ requires C, 65.3; H, 4.8; N, 19.05%), $\nu_{max.}$ 3 344, 3 067, and 1 686 cm^{-1}, $\lambda_{max.}$ 275 nm (log ε 4.38), δ [$(CD_3)_2SO$] 3.83 (3 H, s, OMe), 6.95—8.10 (9 H, m, ArH), 9.35 (1 H, s, CH), and 10.47 (1 H, s, NH).

[6/615 *Received*, 31*st March*, 1976]

TABLE 1

Analytical and physical data for the arylformamidines (7a—d) and the oximes (8a—d) and (9c and d)

		Found (%)				Required (%)				
Compound	M.p. (°C)	C	H	N	Formula	C	H	N	$\lambda_{max.}$/nm (log ε)	$\nu_{max.}$/cm^{-1}
(7a) [a]	103	59.2	4.8	27.8	$C_{10}H_{10}N_4O$	59.4	5.0	27.7	295 (4.17), 285sh (4.14), 240 (3.84)	3 289, 3 185, 3 012, 1 656
(7b) [a]	110	57.05	5.15	23.85	$C_{11}H_{12}N_4O_2$	56.9	5.2	24.15	305sh (4.18), 294 (4.22), 244 (3.91)	3 247, 3 125, 1 653
(7c) [a]	118	68.25	4.55	21.2	$C_{15}H_{12}N_4O$	68.15	4.6	21.2	290sh (4.22), 270 (4.26)	3 268, 3 165, 3 021, 1 650
(7d) [a]	98	65.65	4.85	19.3	$C_{16}H_{14}N_4O_2$	65.3	4.8	19.05	305sh (4.16), 279 (4.26)	3 268, 3 125, 1 650
(8a) [b]	186 [c,d]								253 (4.29)	
(8b) [b]	160	56.8	5.05	23.9	$C_{11}H_{12}N_4O_2$	56.9	5.2	24.15	262 (4.24)	
(8c) [e]	187—189 [d,f]									
(8d) [e]	195—198	65.0	4.7	18.8	$C_{16}H_{14}N_4O_2$	65.3	4.8	19.05	257 (4.32)	
(9c) [g]	155—157 [d,h]									
(9d) [i]	150—152	65.05	4.9	19.15	$C_{16}H_{14}N_4O_2$	65.3	4.8	19.05	254 (4.38)	

[a] From benzene–light petroleum. [b] From aqueous ethanol. [c] Lit.,[6] m.p. 185—186°. [d] Identical with an authentic sample. [e] From ethanol. [f] Lit.,[7] m.p. 185—187°. [g] From chloroform–light petroleum. [h] Lit.,[7] m.p. 138—141° and 147—153°. [i] From benzene.

TABLE 2

^{1}H N.m.r. spectra (δ values) of the arylformamidines (7a—d) [a] and the oximes (8a—d) and (9c and d)

Compound	Solvent	Me	CH	NH	OH	Others
(7a)	$CDCl_3$ [b] *Z*	2.40 (s)	7.98 (d) [c,d]	9.80 (d) [c]		6.9—7.6 (5 H, m, Ph)
	E	2.30 (s)	8.77 (br, s) [e]	[f]		
(7b)	$CDCl_3$ [g] *Z*	2.40 (s)	7.83 (d) [c,d]	9.70 (d) [c]		3.80 (3 H, s, OMe), 6.70—7.35 (4 H, m, ArH)
	E	2.28 (s)	8.65 (br, s) [e]	[f]		3.80 (3 H, s, OMe)
(7c)	$CDCl_3$ [b] *Z*		8.00 (d) [c,d]	9.90 (d) [c]		6.7—8.4 (10 H, m, Ph)
	E		8.76 (br, s) [e]	[f]		
(7d)	$CDCl_3$ [h] *Z*		7.87 (d) [c,d]	9.78 (d) [c]		3.75 (3 H, s, OMe), 6.60—8.45 (9 H, m, ArH)
	E		8.66 (br, s) [e]	[f]		3.72 (3 H, s, OMe)
(8a)	$(CD_3)_2SO$	2.26 (s)	9.26 (s)		11.55 (s)	7.4—8.1 (5 H, m, Ph)
	$CDCl_3$	2.42 (s)	8.65 (s)		9.12 (br, s)	
(8b)	$(CD_3)_2SO$	2.22 (s)	9.11 (s)		11.47 (s)	3.80 (3 H, s, OMe), 6.95—7.95 (4 H, m, ArH)
	$CDCl_3$	2.41 (s)	8.52 (s)		9.65 (s)	
(8c)	$(CD_3)_2SO$		9.28 (s)		11.80 (s)	7.30—7.95 (10 H, m, Ph)
(9c)	$(CD_3)_2SO$		9.46 (s)		11.94 (s)	7.25—8.10 (10 H, m, Ph)
	$CDCl_3$		8.82 (s)		12.20 (s)	
(8d)	$(CD_3)_2SO$		9.15 (s)		11.75 (s)	3.80 (3 H, s, OMe), 6.95—7.90 (9 H, m, ArH)
(9d)	$(CD_3)_2SO$		9.34 (s)		11.85 (br, s)	3.82 (3 H, s, OMe)
	$CDCl_3$		8.65 (s)		11.08 (br, s)	

[a] The *Z* : *E* ratio (n.m.r.) seems unaffected by the method of preparation (see experimental section). [b] *Z* : *E* 1.8 : 1. [c] $J_{CH,NH}$ 13 Hz. [d] Singlet after adding D_2O. [e] $W_{1/2}$ 4—5 Hz. [f] Not observed. [g] *Z* : *E* 2.1 : 1. [h] *Z* : *E* 2.4 : 1.