Mononuclear Heterocyclic Rearrangements. Part 11.[1] Rearrangements of 1,2,4-Oxadiazoles, Isoxazoles, and 1,2,5-Oxadiazoles involving a Sulphur Atom †

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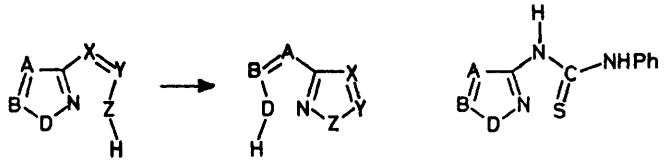
The reactions of 3-amino-5-methyl- and 3-amino-5-phenyl-1.2.4-oxadiazoles, 3-amino-5-methylisoxazole, and 3-amino-4-methyl- and 3-amino-4-phenyl-1.2.5-oxadiazoles with phenyl isothiocyanate have been investigated, and the reactivity of phenylthioureido-derivatives (3) of these ring systems towards rearrangement have been studied. The presence of a sulphur atom in the side-chain sequence (1; XYZ = NCS) greatly enhances the reactivity of the systems under consideration towards rearrangement. The tendency of the three heterocycles to rearrange decreases in the order 1,2,4-oxadiazole > isoxazole > 1,2,5-oxadiazole.

In the context of our research[1,2] on mononuclear heterocyclic rearrangements of the type (1) ⟶ (2),[3] we became interested in how changes in the nature of the heterocycle and the side-chain sequence influence reactivity.

We reported recently that 1,2,4-oxadiazole, isoxazole, and 1,2,5-oxadiazole systems containing the same NCN side-chain sequence show different tendencies to rearrange. This was ascribed to the diverse aromatic characters of the heterocycles considered, and to the different electronic distributions in the O–N bonds being cleaved.[1]

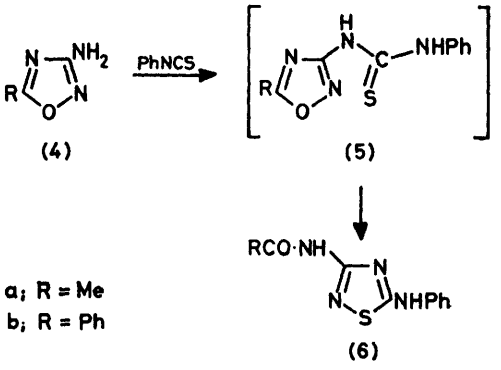
We now report our efforts to synthesize thioureido-derivatives of 1,2,4-oxadiazole (3; ABD = NCO), isoxazole (3; ABD = CCO), and 1,2,5-oxadiazole (3; ABD = CNO), with the aim of confirming the already observed order of rearrangement reactivity of these ring systems.

1,2,4-*Oxadiazole.*—Some of us have already reported[2g] that treatment of the 3-amino-derivatives (4) with phenyl isothiocyanate at 120—130 °C in the absence of solvent gives the rearrangement products (6). To obtain the desired thiourea intermediates, we therefore have explored different experimental conditions. The 3-amino-derivatives (4) did not react with phenyl isothiocyanate in refluxing tetrahydrofuran (THF) or in ethyl acetate. However, when we performed the reaction in dimethylformamide (DMF) at room temperature, although we found no evidence for a significant amount of the intermediate (5) (t.l.c.), we did obtain the rearrangement products (6). This suggests that the thiourea (5) rearranges readily to (6) in this solvent. The same phenomenon occurs in other dipolar aprotic solvents; in dimethyl sulphoxide (DMSO), in fact, after mixing (4a) with phenyl isothiocyanate, the only methyl ^{1}H n.m.r. signal present after a few hours at the temperature of the n.m.r. probe was that of (6a).



(1) (2) (3)

Isoxazole.—Warming the isoxazole (7) carefully at 100 °C with phenyl isothiocyanate in the absence of solvent gave directly the rearrangement product (9). However, when we performed the reaction in DMF or ethyl acetate at room temperature, we were able to isolate the thiourea (8), along with (9).



(4) (5) (6)

The thiourea (8) easily rearranges to (9), either in the presence of a base at room temperature, or at its m.p. The same process takes place in solution and in the absence of base; the nature of the solvent markedly affects the rate of rearrangement. In fact, although in chloroform or benzene it was possible to observe the formation of an appreciable amount of the rearrangement product (by t.l.c. or n.m.r. spectroscopy) only after a long time at room temperature, in protic or dipolar aprotic solvents the rearrangement is much faster. Thus, at room temperature, the process (8) ⟶ (9) is

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[1] Part 10, M. Ruccia, N. Vivona, G. Cusmano, and G. Macaluso, *J.C.S. Perkin I*, 1977, 589.

[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, 4959; (*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, *J. Heterocyclic Chem.*, 1975, **12**, 1327; (*l*) D. Spinelli, A. Corrao, V. Frenna, N. Vivona, M. Ruccia, and G. Cusmano, *J. Heterocyclic Chem.*, 1976, **13**, 357.

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

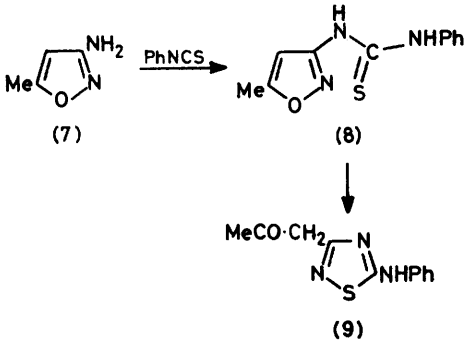
almost complete in ethanol after 20 h, and after only 5—6 h in DMSO.

1,2,5-*Oxadiazole*.—In contrast with the two foregoing heterocyclic systems, thioureido-1,2,5-oxadiazoles (11) could be obtained simply by treating the amine (10) with phenyl isothiocyanate in DMF at room temperature (see Experimental section). In the absence of base, the rearrangement of (11) occurred only slowly, even in a dipolar aprotic solvent. Thus, at room temperature in ethanol or DMSO, only traces of rearrangement products could be detected (by t.l.c. or n.m.r.) after many hours.

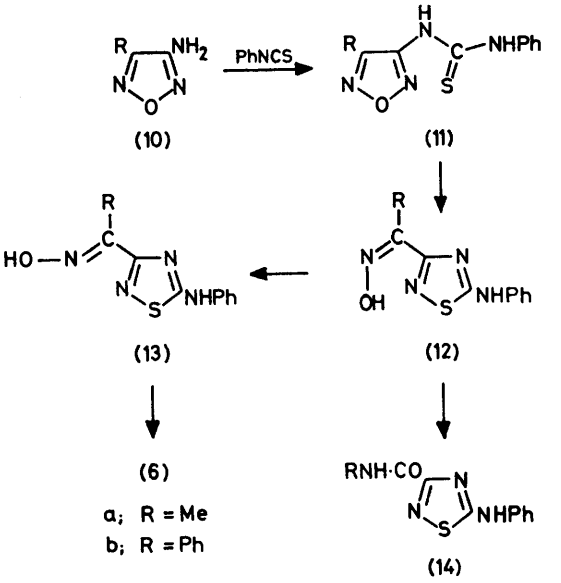
The rearrangement proceeds readily only in the presence of a base. In fact, by adding aqueous potassium hydroxide, in ethanol at room temperature, the thioureas (11) could be transformed easily into the thiadiazoles (12); the exclusive isolation of the *Z*-oximes might be a result of conservation of the geometry present in the starting ring system. Raising the temperature leads to different results: thus (11a) gave the *E*-oxime (13a), whereas the thiourea (11b) gave a 1 : 1 mixture of *Z*-oxime (12b) and *E*-oxime (13b). When the *Z*-oxime (12a) is heated at its m.p., it gives (13a), whereas the *Z*-oxime (12b) generates a 1 : 1 mixture of (12b) and (13b).

The configurations of the oximes were established on the basis of the products of Beckmann rearrangement. As shown in the Scheme, *E*-oximes (13) yield acylamino-derivatives (6), whereas *Z*-oximes (12) give the thiadiazole carboxamides (14).

Conclusion.—Both NCN and NCS sequences are present in the side-chain of the phenylthioureido-derivatives (3). The results so far collected indicate, however, that only the NCS sequence is active in the rearrangement of systems examined. This must be



ascribed to the superior nucleophilic properties of the sulphur atom in attacking the ring nitrogen atom. This is not surprising, since we have already pointed out that the presence of a sulphur atom in the side chain sequence of (1) (*i.e.* Z = S) greatly enhances the rearrangement reactivity of the systems considered. In agreement with our previous studies,[1] the tendency of the three heterocycles to rearrange decreases in the order 1,2,4-oxadiazole > isoxazole > 1,2,5-oxadiazole. Indeed, in the case of 1,2,4-oxadiazole (the most reactive ring) we could not isolate the thioureido-intermediates (5). The ease of rearrangement observed for the 1,2,5-oxadiazole derivatives (11) is noteworthy, since for the same ring system it has been found that transformation occurs only under forcing conditions in the case of other side-chain sequences.[1,3,4]



SCHEME

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).

Reaction of 3-Amino-1,2,4-oxadiazoles (4a *and* b) *with Phenyl Isothiocyanate*.—A solution of the oxadiazole (4a or b) (0.02 mol) in dry DMF (20 ml) and phenyl isothiocyanate (3 ml) was kept at room temperature for 20—30 days. [In the case of (4a), the rearrangement product slowly separated.] After dilution with water, the crude products were filtered off and washed with cold ethanol [(6a)] or ethyl acetate [(6b)] to remove starting material, yielding the product (6a) [2g] (70%), m.p. 278° (from dioxan), or (6b) [2g] (50%), m.p. 214° (from ethanol).

Reaction of 3-Amino-5-methylisoxazole (7) *with Phenyl Isothiocyanate*.—(a) *Without solvent*. A mixture of the isoxazole (7) (0.5 g) and phenyl isothiocyanate (0.9 ml) was carefully heated at 60—70 °C. The temperature was then slowly raised to 100 °C, and kept there for 1 h. After cooling, work-up with the minimum amount of benzene and filtration gave 3-*acetonyl*-5-*anilino*-1,2,4-*thiadiazole* (9) (50%), m.p. 108° (from benzene) (Found: C, 57.0; H, 4.75; N, 18.3. $C_{11}H_{11}N_3OS$ requires C, 56.65; H, 4.75; N, 18.0%); $\lambda_{max.}$ 281 nm (log ε 4.23); $\nu_{max.}$ 3 115 (NH) and 1 718 cm^{-1} (C=O); δ ($CDCl_3$) 2.15 (3 H, s, Me), 3.82 (2 H, s, CH_2), 6.95—7.55 (5 H, m, Ph), and 9.08 (1 H, s, NH). Performing the reaction with higher proportions of (7), or without care in the heating, affords decomposition products.

[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.

(b) *In DMF*. To a solution of the isoxazole (7) (2 g) in dry DMF (10 ml), phenyl isothiocyanate (3 ml) was added, and the solution was set aside at room temperature. After 4 h, addition of cold water (60 ml) caused separation of an oil which slowly solidified. After filtration, the crude product (2.5 g), containing the thiourea (8) and the rearrangement product (9), was treated with the minimum amount of ethanol and filtered. The insoluble fraction contained almost pure thiourea (8) (1 g), whereas in ethanolic solution both (8) and (9) were present (t.l.c.). A sample of (8) obtained by adding light petroleum to a solution of (8) in the minimum amount of benzene at room temperature had m.p. 102—106° (Found: C, 56.8; H, 4.8; N, 18.2. $C_{11}H_{11}N_3OS$ requires C, 56.65; H, 4.75; N, 18.0%); $\lambda_{max.}$ (dioxan) 267 nm (log ε 4.25); $\nu_{max.}$ 3 185 and 3 030 (NH) and 1 190 cm^{-1} (C=S); δ ($CDCl_3$) 2.38 (3 H, s, Me), 5.97 (1 H, s, CH), 7.20—7.75 (5 H, m, Ph), and 10.40 and 11.15 (2 H, 2s, NH).

To a suspension of (8) (0.1 g) in ethanol (2 ml), aqueous 10% potassium hydroxide (0.3 ml) was added; after 5—10 min at room temperature, addition of water (10 ml) and neutralization with acetic acid gave (9) (80%). The same rearrangement takes place even in the absence of base, *e.g.* keeping an ethanolic solution of (8) at room temperature, or refluxing (8) gently in benzene.

Reaction of 3-*Amino*-4-*methyl*-1,2,5-*oxadiazole* (10a) *with Phenyl Isothiocyanate*.—To a solution of the oxadiazole (10a) [5] (4 g) in dry DMF (20 ml), phenyl isothiocyanate (6 ml) was added, and the mixture was kept at room temperature for 8—10 days. Addition of water (200 ml) caused separation of an oil, which slowly solidified. After filtration the dried crude product was dissolved in benzene and an insoluble fraction (rearrangement products) was filtered off. Addition of light petroleum to the benzene solution gave 4-*methyl*-3-*phenylthioureido*-1,2,5-*oxadiazole* (11a) (50%), m.p. 125° (from ethanol) (Found: C, 51.65; H, 4.4; N, 24.15. $C_{10}H_{10}N_4OS$ requires C, 51.3; H, 4.3; N, 23.9%); $\lambda_{max.}$ 268 nm (log ε 4.17); δ ($CDCl_3$) 2.46 (3 H, s, Me), 7.20—7.70 (5 H, m, Ph), and 8.65 and 10.82 (2 H, 2s, NH).

Reaction of 3-*Amino*-5-*phenyl*-1,2,5-*oxadiazole* (10b) *with Phenyl Isothiocyanate*.—To a solution of the oxadiazole (10b) [6] (13 g) in dry DMF (50 ml), phenyl isothiocyanate (30 ml) was added, and the mixture was kept at room temperature for 8—10 days. The solution was then poured into water (600 ml) and the oil which separated was collected and dissolved in ether. The ethereal solution was washed with water, dried, and evaporated under reduced pressure. The oily residue was chromatographed on a dry column of silica gel (300 g), deactivated with water (15%). Elution with cyclohexane–ethyl acetate (95 : 5) gave, in the first 1 700 ml, phenyl isothiocyanate and by-products, further fractions (1 800 ml), gave almost pure 4-*phenyl*-5-*phenylthioureido*-1,2,5-*oxadiazole* (11b) (2.4 g, 10%), m.p. 126—128° (from ethanol) (Found: C, 60.9; H, 4.1; N, 19.05. $C_{15}H_{12}N_4OS$ requires C, 60.8; H, 4.1; N, 18.9%); $\lambda_{max.}$ 254 nm (log ε 4.23); $\nu_{max.}$ 3 247 and 3 145 (NH) and 1 189 cm^{-1} (C=S); δ ($CDCl_3$) 7.20—7.80 (10 H, m, Ph), and 8.05 and 10.75 (2 H, 2s, NH). Elution with cyclohexane–ethyl acetate (80 : 20) removed the amino-compound (10b), some unidentified products, and then 5-*anilino*-3-*benzoyl*-1,2,4-*thiadiazole* Z-*oxime* (12b) (4 g), m.p. 187° (from ethanol) (Found: C, 60.9; H, 4.1; N, 18.8. $C_{15}H_{12}N_4OS$ requires C, 60.8; H, 4.1; N, 18.9%); $\lambda_{max.}$ 265—271 (log ε 4.24) and 236—240 nm (plateau, log ε 4.16); $\nu_{max.}$ 3 175—3 030 cm^{-1} (NH, OH); δ [$(CD_3)_2SO$] 6.95—7.90 (10 H, m, 2Ph), and 11.05 and 11.66 (2 H, 2s, NH, OH). Further elution gave the E-*oxime* (13b) (0.5 g), m.p. 220° (from ethanol) (Found: C, 60.9; H, 4.2; N, 19.2. $C_{15}H_{12}N_4OS$ requires C, 60.8; H, 4.1; N, 18.9%); $\lambda_{max.}$ 236 (log ε 4.29) and 252—260 nm (plateau, log ε 4.24); $\nu_{max.}$ 3 279 and 3 125—3 030 cm^{-1} (NH, OH); δ [$(CD_3)_2SO$] 7.0—7.70 (10 H, m, 2Ph), and 11.10 and 11.98 (2 H, 2s, NH, OH).

Rearrangements of the Thioureas (11a *and* b).—(a) *With base at room temperature*. To a suspension of the thiourea (11a) (3 g) in ethanol (30 ml), aqueous 10% potassium hydroxide (12 ml) was added. The solution was kept at room temperature for 1/2 h; addition of water (100 ml) and neutralization with acetic acid then gave 3-*acetyl*-5-*anilino*-1,2,4-*thiadiazole* Z-*oxime* (12a) (80%), m.p. 188° (from ethanol) (Found: C, 51.25; H, 4.3; N, 24.0. $C_{10}H_{10}N_4OS$ requires C, 51.3; H, 4.3; N, 23.9%); $\lambda_{max.}$ 253 (log ε 4.25) and 296 nm (4.02); $\nu_{max.}$ 3 226 and 3 086 cm^{-1} (NH, OH); δ [$(CD_3)_2SO$] 2.17 (3 H, s, Me), 6.95—7.70 (5 H, m, Ph), and 11.05 and 11.34 (2 H, 2s, NH and OH). By the same procedure, the thiourea (11b) gave the Z-oxime (12b) (60%).

(b) *With base in refluxing solvent*. The above reaction was carried out by heating at reflux in ethanolic solution for 2 h. In the case of (11a) dilution with water and neutralization with acetic acid gave the E-*oxime* (13a) (60%), m.p. 222° (from ethanol) (Found: C, 51.3; H, 4.1; N, 23.95. $C_{10}H_{10}N_4OS$ requires C, 51.3; H, 4.3; N, 23.9%); $\lambda_{max.}$ 240 (log ε 4.33) and 276—288 nm (plateau, log ε 4.03); $\nu_{max.}$ 3 226—3 030 cm^{-1} (NH, OH); δ [$(CD_3)_2SO$] 2.25 (3 H, s, Me), 6.90—7.85 (5 H, m, Ph), and 10.92 and 11.70 (2 H, 2s, NH and OH). In the case of (11b), the same procedure gave a mixture (1 : 1) of (12b) and (13b) which was separated by column chromatography on deactivated silica gel. Elution with cyclohexane–ethyl acetate (9 : 1) gave first (12b), then (13b).

(c) *Heat-induced*. The thiourea (11a or b) (0.2 g) was carefully heated to its m.p. in a preheated oil-bath (130 °C). After melting and solidifying, the sample was removed and the crude products were suitably purified. In the case of (11a), crystallization from ethanol gave the oxime (13a) (60%); in the case of (11b) column chromatography gave (12b) and (13b).

Isomerization of the Z-Oximes (12a *and* b).—The oxime (12a or b) (1 g) was heated at its m.p. After cooling, the crude product was suitably purified. In the case of (12a), we obtained the *E*-oxime (13a) (90%); in the case of (12b), we obtained a 1 : 1 mixture of (12b) and (13b). The same isomerization process has been observed on heating the *Z*-oximes in ethanolic solution in the presence of hydrochloric acid or aqueous potassium hydroxide.

Beckmann Rearrangement of the Oximes (12a *and* b) *and* (13a *and* b).—The oxime (12a) (2 g) in dry chloroform (60 ml) was cooled in an ice-bath, and phosphorus pentachloride (2.5 g) was added. The mixture was kept at room temperature for 2 days and then the solvent allowed to evaporate off slowly at room temperature. The residue was worked up with the minimum amount of ethanol; water was then added, the pH adjusted to 8—9 with ammonium hydroxide, and the mixture extracted with chloroform. The extracts were dried and evaporated and the residue was heated under reflux for 1/2 h with ethanol;

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

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

some insoluble material was filtered off and discarded. The resulting ethanolic solution was evaporated and the residue chromatographed. Elution with cyclohexane–ethyl acetate (2 : 1) removed starting material and decomposition products. Subsequent elution with ethyl acetate gave the *5-anilino-1,2,4-thiadiazole-3-N-methylcarboxamide* (14a) (0.5 g), m.p. 185° (from ethanol) (Found: C, 51.35; H, 4.0; N, 23.85. $C_{10}H_{10}N_4OS$ requires C, 51.3, H, 4.3; N, 23.9%); $\lambda_{max.}$ 246 (log ε 4.16) and 297 nm (3.98); $\nu_{max.}$ 3 333, 3 205, and 3 145 (NH), and 1 650 cm^{-1} (C=O); δ [$(CD_3)_2SO$] 2.82 (3 H, d, NH*Me*, *J* 4.5 Hz), 6.80—7.80 (5 H, m, Ph), 8.60 (1 H, q, N*H*Me, *J* 4.5 Hz), and 11.35br (1 H, s, NH).

In the cases of (12b) and (13a and b), the mixture of oxime (0.005 mol) in chloroform (60 ml) and phosphorus pentachloride (0.01 mol) was kept at room temperature for 12 h and then left to evaporate spontaneously. The residue was worked up with the minimum amount of ethanol, then water was added, and the crude product was filtered off and washed with water. The product from (13a) was refluxed in ethanol (50 ml) and then filtered off. The insoluble fraction, crystallized from dioxan, gave (6a) (50%). The crude products from (13b) and (12b) were dissolved in boiling ethanol. After cooling, the product was filtered off and recrystallized from ethanol, giving (6b) (50%) or the *anilide* (14b) (50%), m.p. 229° (from ethanol) (Found: C, 61.1; H, 4.0; N, 19.1. $C_{15}H_{12}N_4OS$ requires C, 60.8; H, 4.1; N, 18.9%); $\lambda_{max.}$ 265 nm (log ε 4.43); $\nu_{max.}$ 3 356 and 3 236 (NH) and 1 695 cm^{-1} (C=O); δ [$(CD_3)_2SO$] 6.90—7.90 (10 H, m, 2Ph) and 10.38 and 11.10 (2 H, 2s, NH).

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