Mononuclear Isoheterocyclic Rearrangements. Note I. Interconversion of 3-Benzoylamino-5-methyl-1,2,4-oxadiazole and 3-Acetylamino-5-phenyl-1,2,4-oxadiazole

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The first example of mononuclear isoheterocyclic rearrangement is reported. The 3-benzoylamino-5-methyl-1,2,4-oxadiazole (**5**) furnishes through a reversible process (slowly at room temperature in methanol, acetone or dioxane, fast in DMSO or in methanol in the presence of strong bases) a mixture of **5** and 3-acethylamino-5-phenyl-1,2,4-oxadiazole (**6**). The equilibrium process can be achieved also by heating **5** at 181° and the same reaction mixture can be obtained using **6** as the starting material. 3-Trichloroacetylamino-5-methyl-1,2,4-oxadiazole (**7**) was unaffected by similar treatment. The results obtained are discussed.

Boulton, Katritzky and Hamid (1) have proposed a generalized scheme which covers every possible case of mononuclear heterocyclic rearrangements (m.h.r.'s) without indicating any limitation on the nature of atoms *A*, *B*, *D*, *X* and *Z*.

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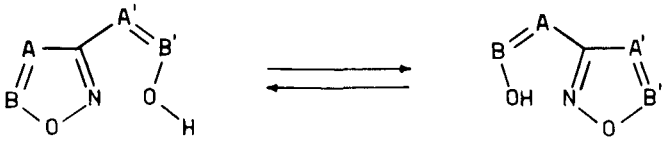
An accurate examination of the above scheme induces us to suggest two restrictive conditions relative to the nature of *D* and *Z* atoms in the starting heterocycle and in the side chain. The first one is that *D* must be an atom or group which has to behave as more electronegative than the adjacent *N* (2) and so the *D-N* bond must have predominantly a single-bond character. The second one is that *Z* must be a good nucleophilic center in the reaction conditions (its actual nucleophilicity can be increased by basic catalysis or by the use of dipolar aprotic solvent). The m.h.r.'s seem to be a special type of internal nucleophilic substitution in which *Z* is the nucleophile, *N* the reaction center, and *D* the leaving group. As a consequence, the leaving group ability of *D* becomes an important factor.

We have observed that, in accordance with the first restrictive condition, literature reports cases of realized rearrangements only for *D* = *O* (3,4). (Thus it is evident that the reaction scheme can represent a reversible reaction only for *Z* = *O*). The calculated electronic densities in the starting rings studied [isoxazole (5), 1,2,4-oxadiazole (5,6), and 1,2,5-oxadiazole (5)] have indicated a low π-character in the *N-O* bond and a σ-density on *O* higher than on *N* (7).

According to the second condition *Z* (8) can be *O* (1,9), *S* (10), *Se*, *N* (1,11) or *C* (12) [in anionic form and eventually in solution of dipolar aprotic solvents (12)].

Continuing our research in this field (10-12) we have now directed our attention to *iso-m.h.r.'s* eventually reversible. It can be seen from the above discussion that the Boulton scheme can be modified thus:



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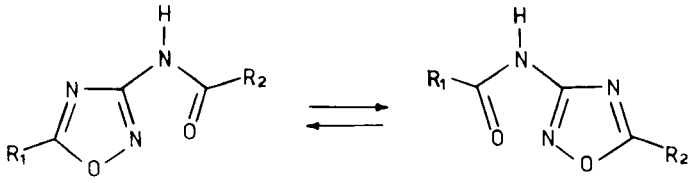
The symbolism used indicates that the atoms (*A* and *B*) present in the ring of the starting product **3** are the same as those of the side chain (*A'* and *B'*) whereas the substituents on them can differ in the two cases. Some attempts to realize an *iso-m.h.r.* have been made by other AA. *E.g.*, Boulton (4) failed to rearrange the oxime of 3-benzoyl-5-methyl-1,2,5-oxadiazole into the oxime of 3-acetyl-4-phenyl-1,2,5-oxadiazole, in spite of the forecast based on the relative stability of the two products. On the other hand Ponzio and Biglietti (13) reported the rearrangement

of the dioxime of 3,4-dibenzoyl-1,2,5-oxadiazole into the dioxime of 3-phenyl-4-benzoylformyl-1,2,5-oxadiazole achieved by heating or by action of 20% aqueous sodium hydroxide.

In this paper we report data on the first case of *iso-m.h.r.'s* realized on derivatives of 1,2,4-oxadiazole, a system which is well known to be prone to giving the normal *m.h.r.'s* easily (1,9-12).

Chemical Data.

The products tested to ascertain the existence of the equilibrium **3** ⇌ **4** in different experimental conditions were the compounds **5** and **6**.



5 **6**

7 **8**

$R_1 = CH_3$; $R_2 = C_6H_5$

$R_1 = CH_3$; $R_2 = CCl_3$

3-Benzoylamino-5-methyl-1,2,4-oxadiazole (**5**, m.p. 144°) on heating at 181-183° for 1 minute gave an equilibrium mixture, which, analyzed by nmr, was shown to contain 13.5% of **5** and 86.5% of **6**. The same equilibrium mixture was obtained by heating the 3-acetylamino-5-phenyl-1,2,4-oxadiazole (**6**, m.p. 164°) in the same experimental conditions. The composition of the equilibrium mixture seemed unaffected by the heating time (1 and 10 minutes). The result obtained allowed us to calculate the following thermodynamic data for the equilibrium studied: $K_{182°} = 6.4$, $\Delta G°_{182°} = -1.7$ kcal/mol, which indicated that the thermodynamically favored spontaneous process was the one from **5** to **6**.

We observed the same equilibrium process also in solution, the nature of solvent affecting largely the rate of the rearrangement but scarcely the value of the equilibrium constant. In fact, following the process at room temperature with nmr techniques, it was possible to observe, using **5** as the starting material, the presence of an appreciable amount of **6** (5-10% of transformation) after only a few hours in DMSO, or only after a long time (100 hours or more) in acetone, dioxane or methanol. The value of the equilibrium constant is only slightly affected by the nature of the solvent used ($K_{25°} = 6 \div 10$) (14), as one could foresee, taking into account the fact that the equilibrium position is controlled by the relative thermodynamic stability of compounds **5** and **6** in the solvent used, which is a function of the heats of formation and solvatation of **5** and **6**, where the first term undoubtedly plays a more important role.

We also observed that the rearrangement studied is largely catalyzed by addition of base. In fact, by means of the same nmr technique, it was possible to observe that **5** in DMSO or perdeuteriomethanol, in the presence of catalytic amount of potassium *t*-buthoxide and at room temperature, after 10 minutes gave about 60% or 30% of **6** respectively.

To gain information about the influence of the substituent present in the side chain (the moiety similar to a nucleophilic reagent, see above) we submitted the 3-trichloroacetylamino-5-methyl-1,2,4-oxadiazole (**7**) to heating either above its melting point or in solution (DMSO) with and without the presence of a catalytic amount of potassium *t*-buthoxide. In every case we recovered **7** unchanged, without any trace of the product of rearrangement (3-acetylamino-5-trichloromethyl-1,2,4-oxadiazole, **8**) thus putting in evidence the important role played by the substituent present in the side-chain.

Discussion of Results.

The results obtained require some comment in an attempt to understand the factors which affect the position of equilibrium and also the possibility of the reaction occurring. In accordance with the previous discussion, an *iso-m.h.r.* occurs if the oxygen atom of the side-chain has a high electronic density (and thus a nucleophilic character) so that it can carry its nucleophilic attack to the nitrogen of the ring. In the reactions studied by us the high electronic density on the amidic oxygen of the side chain was determined by the adjacent nitrogen, which assists the reaction with its electromeric effect.

A good indication of the electronic density of the oxygen atom can be obtained by comparing the values of carbonyl stretching vibrations for **5**, **6** and **7**. The values observed [$(\nu_{C=O})_5 = 1658$ cm^{-1}, $(\nu_{C=O})_6 = 1695$ cm^{-1}, and $(\nu_{C=O})_7 = 1724$ cm^{-1}] indicated an increase of the double bond character of carbonyl and thus a decrease of electronic density on the oxygen atom, going from **5** to **6** and then to **7**. As a result we observed no reaction in the case of **7**, and a lower reactivity for **6** than for **5**.

An interpretation of the data obtained can also be derived from the forseeable influence that the substituents present in the ring and in the side-chain of starting and final products must have on the relative thermodynamic stability of the two products. Other factors being equal, a phenyl group present on the 1,2,4-oxadiazole ring (at C_5) increases the stability more than a methyl group. In fact the resonance stabilisation energy of the diaryloid system (5-phenyl-1,2,4-oxadiazole) is greater than that of the 5-methyl-1,2,4-oxadiazole (15). As a consequence **6** is thermodynamically more stable than **5**, and this fact affects the equilibrium position ($K_{5 \rightleftharpoons 6} = 6 \div 10$) (14,16).

Finally we should remark that the rate of the reaction is largely affected by the properties of the solvent used. In DMSO (a dipolar aprotic solvent, which by its nature enhances the rate of nucleophilic reactions) the rate of the reactions is high, whereas in methanol (an amphiprotic solvent, which solvates the nucleophilic centers, thus decreasing their reactivity) and in acetone or dioxane (aprotic solvents of decreasing polarities with respect to DMSO) the rate is low.

EXPERIMENTAL

Melting points were determined using a Kofler hotplate and are uncorrected. Ir spectra (Nujol mull) were determined on a Perkin-Elmer Infracord 137 instrument. Nmr spectra (60 MHz) were determined on a Jeol C-60H spectrometer with TMS as internal standard.

3-Benzoylamino-5-methyl-1,2,4-oxadiazole (**5**).

A suspension of 3-amino-5-methyl-1,2,4-oxadiazole (4 g.), anhydrous benzene (300 ml.), benzoyl chloride (5 ml.) and anhydrous pyridine (4 ml.) was allowed to stand at room temperature for 20-30 days and then (tlc showed the absence of the amino compound) was evaporated to dryness under reduced pressure. Water (60 ml.) was added to the residue, worked up and then filtered and washed with water. Crystallization from benzene gave **5** (4 g.). An analytical sample was crystallized from benzene (17): m.p. 144°; ir: 3106 cm^{-1} (NH), 1658 cm^{-1} (C=O); nmr (DMSO): δ 2.58 (s, 3H, CH_3), 7.30-8.15 (m, 5H, ArH), 11.36 (s, 1H, NH).

Anal. Calcd. for $C_{10}H_9N_3O_2$: C, 59.10; H, 4.46; N, 20.68. Found: C, 59.20; H, 4.50; N, 20.75.

3-Acetylamino-5-phenyl-1,2,4-oxadiazole (**6**).

Acetic anhydride (2.5 ml.) was added to a solution of 3-amino-5-phenyl-1,2,4-oxadiazole (2 g.) in anhydrous benzene (50 ml.) and the mixture was heated under reflux for 25-30 hours. The solvent was evaporated under reduced pressure and the residue worked up with light petroleum and filtered. Crystallization from benzene gave **6** (1.5 g.). An analytical sample was crystallized from ethanol (17), m.p. 164° [lit. m.p. 160-164° (18), m.p. 150-152° (19)]; ir 3175, 3125 cm^{-1} (NH), 1695 cm^{-1} (C=O); nmr (DMSO-d_6): δ 2.13 (s, 3H, CH_3), 7.55-8.30 (m, 5H, ArH), 11.15 (br. s, 1H, NH).

Anal. Calcd. for $C_{10}H_9N_3O_2$: C, 59.10; H, 4.46; N, 20.68. Found: C, 59.25; H, 4.30; N, 20.50.

3-Trichloroacetylamino-5-methyl-1,2,4-oxadiazole (**7**).

This compound was obtained by the same procedure used for **5**, from 3-amino-5-methyl-1,2,4-oxadiazole (2 g.), anhydrous benzene (200 ml.), trichloroacetyl chloride (2.5 ml.) and anhydrous pyridine (2 ml.) at room temperature for 3 days. Crystallization first from benzene and then from benzene-ligroin (1:1) gave **7** (2.5 g.), m.p. 127°; ir: 3226, 3175 cm^{-1} (NH), 1724 cm^{-1} (C=O); nmr (deuteriochloroform): δ 2.60 (s, 3H, CH_3), 8.95 (s, 1H, NH).

Anal. Calcd. for $C_5H_4Cl_3O_2$: C, 24.56; H, 1.65; N, 17.19. Found: C, 24.50; H, 1.50; N, 17.10.

The trichloroacetylamino **7** was unchanged after: a) heating at 140° for ½ hour; b) heating at 60° in DMSO-d_6 solution for ½ hour (nmr test); and c) heating at 50° for ½ hour in DMSO-d_6 solution with catalytic amount of potassium *t*-butoxide (nmr test).

Thermal Isomerization of **5** and **6**. Equilibrium Mixture.

Tubes containing **5** or **6** (50 mg.) were immersed in a bath at temperature of 181-183°. After fusion the samples were maintained in the bath for 1 minute (first experiment) and 10 minutes (second experiment). After cooling, DMSO-d_6 (0.6 ml.) was added and the nmr spectra recorded. The composition of equilibrium mixture was determined by integration (repeated 6 times) of the singlet at 2.13 δ (CH_3 of **6**) and the multiplet for aromatic protons (ArH = 10H for **5** and **6**). The singlet at 2.58 δ (CH_3 of **5**) was neglected for integration because of proxymity of DMSO-d_6 signals. The results obtained from two independent experiments, showed the composition of equilibrium mixture: 13.5% of **5** and 86.5% of **6**.

Isomerization of **5** in DMSO-d_6 Solution with Potassium *t*-Butoxide.

To a solution of **5** in DMSO-d_6 in an nmr tube, catalytic amounts of potassium *t*-butoxide was added and the nmr spectrum recorded. As soon as the first spectrum was recorded at room temperature, *ca.* 10% of **6** was present. After 10 minutes, by the same procedure for integration, 60 ± 5% of **6** was present.

Isomerization of **5** in Perdeuteriomethanol with Potassium *t*-Butoxide.

The same technique was used. After 10 minutes, by integration of the singlet at 2.20 δ (CH_3 of **6**) and the singlet at 2.57 δ (CH_3 of **5**), 30 ± 5% of **6** was present.

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

(2) The ability of the *N* atom to undergo nucleophilic attack by *Z* can be increased by means of electrophilic catalysis which changes electronic density on the ring of the starting product.

(3) It is not possible to exclude that *m.h.r.'s* happens when $D \neq O$ (*e.g.*, nitrogen linked to strong electron attracting and/or withdrawing groups). Researches on this point are in progress.

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(6) L. Paoloni and M. Cignitti, *Tetrahedron*, **24**, 485 (1968).

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(8) In the reported cases, *m.h.r.'s*, which usually have large interest from a preparative viewpoint, are indicated as irreversible.

(9) Recently it has been reported the rearrangement of 3-(2-hydroxyphenyl)-1,2,4-oxadiazoles into 3-acylaminobenzisoxazoles [K. Harsanyi, *J. Heterocyclic Chem.*, 10, 957 (1973)]. However, the behaviour of the compounds cited was affected by the presence of a benzo condensed system.

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(11a) M. Ruccia and D. Spinelli, *Gazz. Chim. Ital.*, **89**, 1654 (1959); (b) M. Ruccia and N. Vivona, *Ann. Chim. (Italy)*, **57**, 680 (1967); (c) M. Ruccia and N. Vivona, *Chem. Commun.*, 866 (1970); (d) M. Ruccia, N. Vivona, and G. Cusmano, *J. Heterocyclic Chem.*, **8**, 137 (1971).

(12a) M. Ruccia, N. Vivona, and G. Cusmano, *Tetrahedron Letters*, 4959 (1972); (b) M. Ruccia, N. Vivona, and G. Cusmano, *Tetrahedron*, **30**, 3859 (1974).

(13) G. Ponzio and F. Biglietti, *Gazz. Chim. Ital.*, **63**, 159 (1933).

(14) M. Ruccia, N. Vivona, G. Cusmano, M. L. Marino, and D. Spinelli, presented at a meeting of the "Societa Chimica Italiana", Messina (Italy), 28th November, 1974.

(15) An indirect spectroscopic (uv) confirmation of this statement is given by the λ max values measured in cyclohexane for 3-amino-5-methyl-1,2,4-oxadiazole (λ max = 218 nm) and 3-amino-5-phenyl-1,2,4-oxadiazole (λ max = 233 nm) which indicate a more extended conjugation in the 5-phenyl derivative.

(16) The difference in the resonance stabilization energy between two separate benzene rings and biphenyl has been evaluated *ca.* 2-3 kcal/mol. This value well compares to the ΔG° value measured by us for the equilibrium **5** ⇌ **6**.

(17) Tlc and nmr tests revealed the purity of the samples.

(18) G. Wesphal and R. Schmidt, *Z. Chem.*, **14**, 94 (1974).

(19) P. Adams, D. W. Kaiser, and G. A. Peters, *J. Org. Chem.*, **18**, 934 (1953). A tlc test of the described product (m.p. 150-152°) indicated that it is a mixture of **6** and unchanged 3-amino-5-phenyl-1,2,4-oxadiazole, which can be purified by repeated crystallization.