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SYNTHESIS OF THE AMIDES AND ACID HALIDES OF 1,2,4-OXADIAZOLE-3-CARBOHYDROXAMIC ACID

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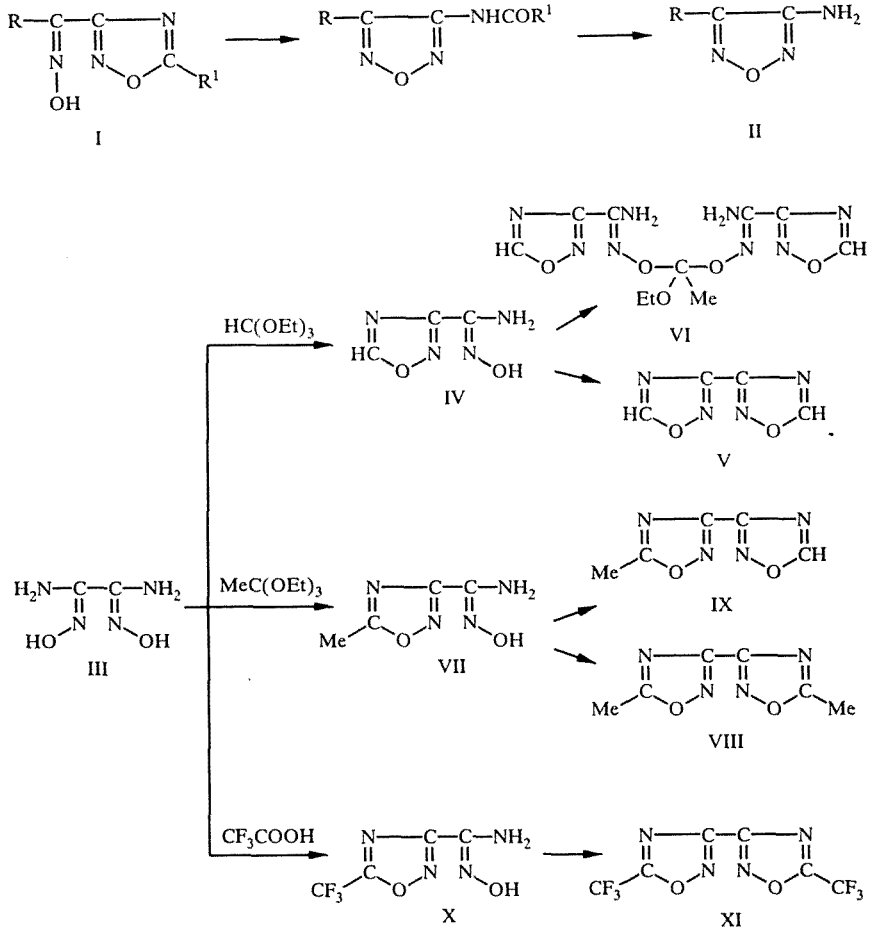
The reaction of diaminoglyoxime with carboxylic acid derivatives gave the amidoximes of 1,2,4-oxadiazole-3-carboxylic acid. It has been found that in the nitrozation of the obtained amidoximes in a solution of hydrochloric or hydrobromic acid the corresponding halooximes are formed.

Derivatives of 1,2,4-oxadiazole, which contain heteroallyl fragments in position 3, are easily rearranged with opening of the oxadiazole ring and formation of another, mostly the 1,2,5-oxadiazole, 1,2,3-triazole, or 1,2,5-thiadiazole rings [1]. In particular, rearrangement of the oximes of 3-acyl-1,2,4-oxadiazoles (I) gives derivatives of amino-1,2,5-oxadiazole (II) [1, 2].



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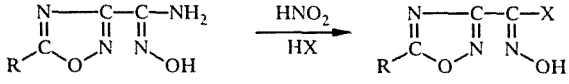
If the possibility exists of varying the substituent R at the oxime group in the initial oxadiazole I, amino-1,2,4-oxadiazoles with the corresponding substituent in the ring can be obtained. The acid halides of the carbohydroxamic acids are promising starting materials for the synthesis of a similar species of functionally substituted oximes. They are dehydrohalogenated by bases with the formation of nitrile oxides, which react readily with different nucleophiles; this gives oximes, containing amino, azido, alkoxy, mercapto, and other groups [3]. Nevertheless, the literature describes only the derivatives of 1,2,4-oxadiazole which contain the halooxime group in position 5 [4].

In the synthesis of the acid halides of 1,2,4-oxadiazole-3-carboxylic acids we started from the corresponding amides. The latter were obtained from the diaminoglyoxime III. In the presence of a catalyst (boron trifluoride etherate) the reactions of diaminoglyoxime with the ethyl ester of orthoformic [5] or orthoacetic acid proceed only via one amidoxime group when a twofold excess of the orthoester is used. When the reaction time is increased and larger amounts of the orthoester are used, both groups react with the formation of the bisoxadiazoles V and VIII. The reactivity of the ethyl orthoacetate is significantly lower than that of ethyl orthoformate. This is probably due to the fact that the reaction of the amidoxime IV with a small excess of ethyl orthoacetate gave the orthoester VI, not the bisoxadiazole IX. On the other hand in the reaction of the amidoxime with ethyl othoformate the bisoxadiazole IX is formed readily and with a high yield.

The reaction of diaminoglyoxime with the trifluoroacetic anhydride cannot be stopped at the stage of formation of the amidoxime X; it proceeds via both groups and leads to the bisoxadiazole XI. The amidoxime X was obtained by refluxing diaminoglyoxime in trifluoroacetic acid. The bisoxadiazole XI is formed simultaneously.

When studying the nitrozation of the amidoximes in a solution of hydrochloric or hydrobromic acid, we have found that the oximes are not destroyed as assumed earlier; instead, the halooximes XII-XV are formed with good yields.



XII–XV

XII R = H, X = Cl; XIII R = Me, X = Cl; XIV R = CF_3, X = Cl; XV R = CF_3, X = Br

EXPERIMENTAL

The PMR spectra were taken on a Bruker WH-90 spectrometer in DMSO-d_6, with TMS as the internal standard. The IR spectra were taken on a Perkin-Elmer 580 B spectrometer in Nujol. The elemental analysis data for C, H, and N corresponded to the calculated values.

5-Methyl-1,2,4-oxadiazole-3-carboxyamidoxime (VII, $C_4H_6N_4O_2$). A suspension of 1.18 g (10 mmoles) of diaminoglyoxime III in 2.43 g (15 mmoles) triethyl orthoacetate and 0.02 ml boron trifluoride etherate were heated at 70-80°C for 10 min. The reaction mixture is cooled, treated with 20 ml ether, and the precipitate filtered off. Yield 1.31 g (92%) of oxadiazole VII with mp 173-175°C (from water). PMR spectrum: 2.56 (3H, s, CH_3), 5.80 (2H, s, NH_2), 10.24 ppm (1H, s, OH). IR spectrum: 3470 and 3370 (NH_2), 1665 cm^{-1} (C=N).

5-Trifluoromethyl-1,2,4-oxadiazole-3-carboxyamidoxime (X, $C_4H_3F_3N_4O_2$). A solution of 11.8 g (100 mmoles) of diaminoglyoxime III in 40 ml trifluoroacetic acid is refluxed for 6 h. The reaction mixture is evaporated in vacuum, ether is added and the unreacted diaminoglyoxime filtered off. The ether solution is washed with 5% $NaHCO_3$ and dried over Na_2SO_4. The ether is stripped off, yield 5.85 g (30%) of oxadiazole X with mp 132°C (from 2-propanol). PMR spectrum: 6.13 (2H, s, NH_2), 10.62 ppm (1H, s, OH). IR spectrum: 3430 and 3320 (NH_2), 1670 (C=N), 1140-1210 cm^{-1} (CF_3).

Bis(1,2,4-oxadiazol-3-yl) (V, $C_4H_2N_4O_2$). A suspension of 9.0 g (76 mmoles) of diaminoglyoxime III in 30 ml triethyl orthoformate and 0.1 g boron trifluoride etherate is heated at 70-80°C for 30 min. The reaction mixture is cooled and the precipitate filtered off. Yield 9.2 g (87%) of oxadiazole V with mp 137°C (from water) (136°C [6]). PMR spectrum: 9.96 ppm (1H, s, CH). IR spectrum: 3111 cm^{-1} (ring CH).

5,5'-Dimethylbis(1,2,4-oxadiazol-3-yl) (VIII, $C_6H_6N_4O_2$). A suspension of 1.18 g (10 mmoles) diaminoglyoxime III in 10 ml triethyl orthoacetate and 0.02 ml boron trifluoride etherate is heated at 80-100°C for 1 h. The reaction mixture is cooled and the precipitate filtered off. Yield 1.50 g (90%) of oxadiazole VIII with mp 166-167°C (from water) (165-166°C [7]). PMR spectrum: 2.67 ppm (3H, s, CH_3).

Orthoester VI ($C_{10}H_{14}N_8O_5$). A mixture of 1.0 g (7.8 mmoles) of amidoxime IV, 2 ml triethyl orthoacetate and 0.02 g boron trifluoride etherate was heated at 100°C for 10 min. The reaction mixture is cooled, treated with 20 ml ether, and the precipitate filtered off. Yield 0.8 g (63%) of orthoester VI with mp 136-138°C (from water). PMR spectrum: 1.00 (3H, t, CH_3), 1.62 (3H, s, CH_3), 3.62 (2H, qu, CH_2), 6.33 (4H, s, NH_2), 9.60 ppm (2H, s, CH). IR spectrum: 3480, 3451, 3379, 3301 (NH_2), 3178 (ring CH), 1642 cm^{-1} (C=N).

5-Methylbis(1,2,4-oxadiazol-3-yl) (IX, $C_5H_4N_4O_2$). A suspension of 1.42 g (10 mmoles) of amidoxime VII in 5 ml triethyl orthoformate and 0.02 ml boron trifluoride etherate is heated at 100°C for 10 min. The reaction mixture is evaporated in vacuum. Yield 1.3 g (86%) of bisoxadiazole IX with mp 77-79° (from ethanol). PMR spectrum: 2.67 (3H, s, CH_3), 9.87 ppm (1H, s, CH). IR spectrum: 3115 cm^{-1} (ring CH).

5,5'-Trifluoromethylbis(1,2,4-oxadiazol-3-yl) (XI, $C_6F_6N_4O_2$). Diaminoglyoxime (1.77 g, 15 mmoles) is added in batches with stirring to 10 ml trifluoroacetic anhydride and the mixture kept at 35-38°C for 2 h. The reaction mixture is evaporated in vacuum, treated with 10 ml water and the precipitate filtered off. Yield 2.65 g (64%) of oxadiazole XI with mp 99-100°C (from ethanol). Mass spectrum (70 eV): 274 (M^+), 255 (M^+-F), 179 ($M^+-CF_3C=N$). IR spectrum: 1608 (oxadiazol), 1150-1250 cm^{-1} (CF_3).

General Method for the Synthesis of Halooximes XII-XV. A solution of 17 mmoles of the corresponding amidoxime in 20 ml hydrochloric or hydrobromic acid is treated dropwise with stirring at 0-5°C with a solution of 1.65 g (24 mmoles) sodium nitrite in 4 ml water. The precipitate is filtered off after 30 min.

1,2,4-Oxadiazol-3-carbohydroximoyl Chloride (XII, $C_3H_2ClN_3O_2$). mp 170-171°C. PMR spectrum: 9.64 (1H, s, CH), 13.27 ppm (1H, s, OH). IR spectrum: 3200 (OH), 3120 (CH), 1617 cm^{-1} (C=N); yield 68%.

5-Methyl-1,2,4-oxadiazole-3-carbohydroximoyl Chloride (XIII, $C_4H_4ClN_3O_2$). mp 152-154°C. PMR spectrum: 2.32 (3H, s, CH_3), 12.0 ppm (1H, s, OH). IR spectrum: 3200 (OH), 1600 cm^{-1} (C=N); yield 64%.

5-Trifluoromethyl-1,2,4-oxadiazol-3-carbohydroximoyl Chloride (XIV, $C_4HClF_3N_3O_2$). mp 176-177°C. PMR spectrum: 11.7 ppm (1H, s, OH). IR spectrum: 3360 (OH), 1620 (C=N), 1150-1280 cm^{-1} (CF_3); yield 61%.

5-Trifluoromethyl-1,2,4-oxadiazol-3-carbohydroximoyl Bromide (XV, $C_4HBrF_3N_3O_2$). mp 134-135°C. PMR spectrum: 11.78 ppm (1H, s, OH). IR spectrum: 3370 (OH), 1615 (C=N), 1170-1225 cm^{-1} (CF_3); yield 66%.

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