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RING FORMATION REACTIONS OF 4-AMINOFURAZAN-3-CARBOXYAMIDOXIMES

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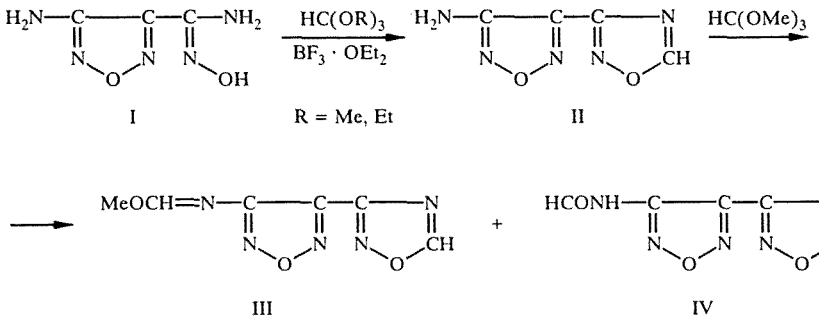
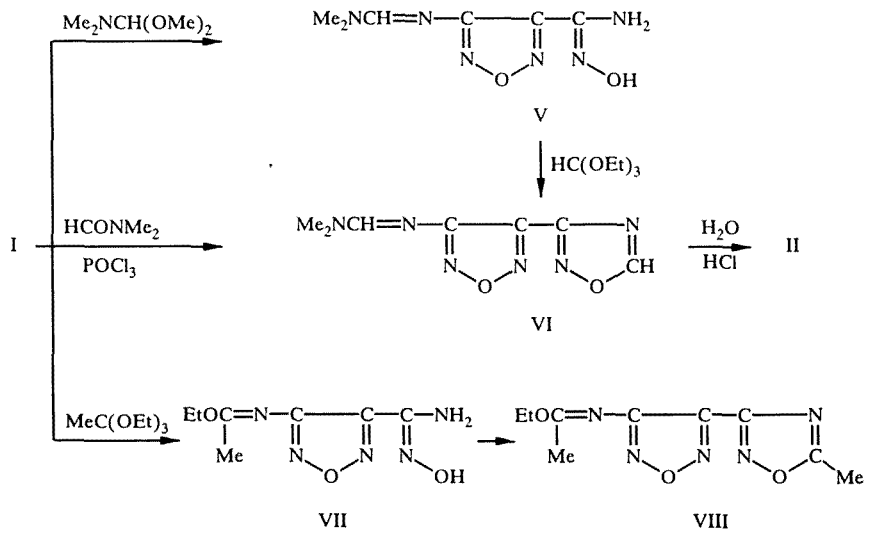
The ring formation of 4-aminofurazan-3-carboxyamidoximes in the reaction with the orthoesters and derivatives of formic and acetic acids leads to the closure of the 1,2,4-hydroxydiazole as well as the pyrimidine ring.

In the reaction with derivatives of carboxylic acids amidoximes form 1,2,4-hydroxydiazole rings [1]; however, the reaction of 4-aminofurazan-3-carboxyamidoxime (I) with formic acid leads to a derivative of furazano[3,4-d]pyrimidine [2]. When studying the reaction of the amidoxime I with the esters of orthoformic acid in the presence of a catalyst (boron trifluoride etherate) we have found that the reaction proceeds at very mild conditions (at room temperature), but leads to the closure not of the pyrimidine but of the 1,2,4-oxadiazole ring with the formation of the amino derivative II:



Heating of the amidoxime I with the more reactive methyl ester leads to the iminoester III, which hydrolyzes partially to the formyl derivative IV.



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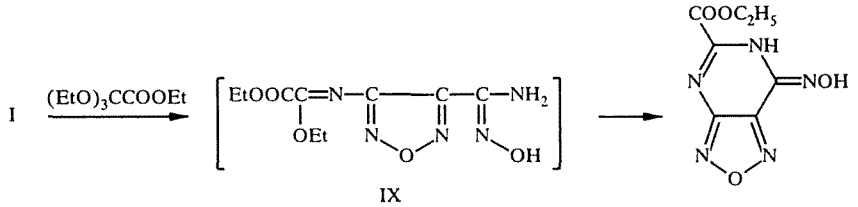
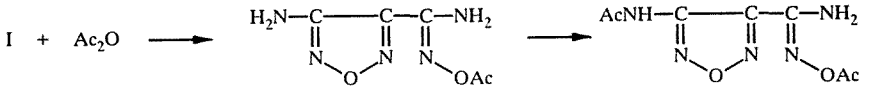
The reactions of the amidoxime I with the dimethylacetal of dimethylformamide and the orthoformic acid ester proceed primarily via the amino group in position 4 of the furazan ring. The amidine V and the iminoester VII, formed at these conditions, cyclize in the further reaction with the orthoester to the oxadiazoles VI and VIII. By using Wilsmeyer's reagent (dimethylformamide + phosphorus oxychloride) at severe conditions, the amidoxime I reacts via both groups and gives directly the furazanyloxadiazole VI. In an acidic medium the formamidine group in compound VI hydrolyzes readily with the formation of the amino derivative II.

Apparently in the same way proceeds the reaction of the amidoxime I with the ethyl ester of the triethoxyacetic acid; however, the iminoester IX, formed in the first stage, in distinction from the derivatives V and VII does not react with the second molecule of the orthoester; instead, it undergoes intramolecular ring formation to the furazanopyrimidine X:



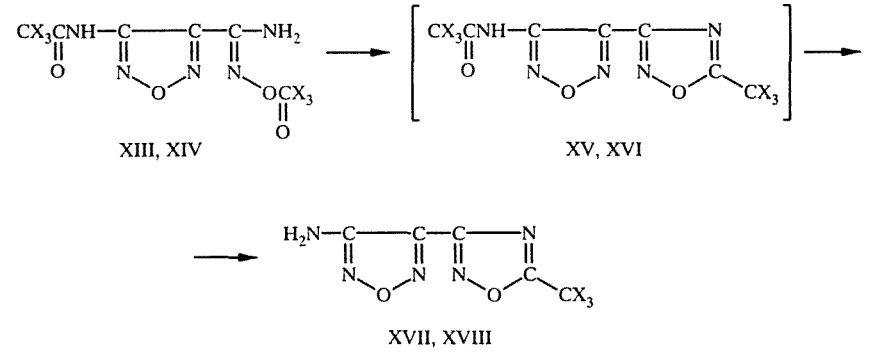
IX X

By the action of acetic anhydride the oxime and amino groups in the amidoxime I are acylated consecutively; however, the thermal cyclization of the O-acetyl derivatives XI and XVII to 1,2,4-oxadiazole did not succeed.



XI XII

The N,O-diacyl derivatives XIII and XIV, which are easily formed in the reaction of the amidoxime I with the trifluoroacetic acid anhydride or trichloroacetyl chloride (in the latter instance the intermediate compound XIV was not separated), when heated form the 5-trihalomethyl-1,2,4-oxadiazoles XV and XIV, the trihaloacetamide group of which is readily hydrolyzed with the formation of the aminofurazanyloxadiazoles XVII and XVIII:

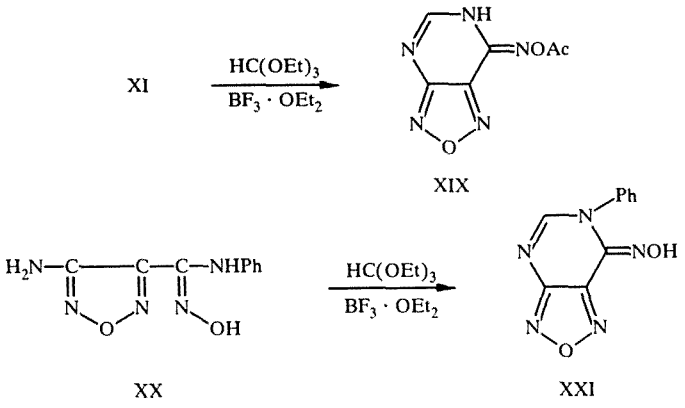


XIII, XIV XV, XVI

XVII, XVIII

XIII, XV, XVII X = F; XIV, XVI, XVIII X = Cl

In the instances when substituents are present in the amidoxime group which prevent closure of the oxadiazole ring, the reaction with the triethylorthoformate leads to the formation of the pyrimidine ring:



EXPERIMENTAL

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

3-(4-Aminofurazanyl-3)-1,2,4-oxadiazol (II, $C_4H_3N_5O_2$). A. A suspension of 1.43 g (10 mmoles) of amidoxime I in 10 ml triethyl orthoformate and 0.02 g boron trifluoride etherate is stirred at room temperature until dissolution of the deposit is complete. After 3 h the reaction mixture is evaporated in vacuum, ether is added to the remaining mixture, and the deposit filtered off. Yield 1.1 g (72%) oxadiazole II.

The reaction with trimethylorthoformate is carried out in the same way. The excess of the orthoester is stripped in vacuum without heating. Yield of oxadiazole II 88%.

B. A suspension of 1.43 g (10 mmoles) amidoxime I in 4.0 ml triethylorthoformate and 0.02 g boron trifluoride etherate is heated for 10 min at 70-80°C and cooled. The deposit is filtered off. Yield 1.2 g (78%) oxadiazole II.

C. A solution of 0.70 g (3.4 mmoles) of amidine IX in 10 ml 5%-hydrochloric acid is refluxed for 10 min. The reaction mixture is cooled and the deposit filtered off. Yield 0.38 g (74%) of oxadiazole II, with characteristics identical to those obtained for the compound prepared by method A; mp 126-127°C (from water). PMR spectrum: 6.40 (2H, s, NH_2), 9.94 ppm (1H, s, CH). IR spectrum: 3480 and 3320 (NH_2), 3120 (ring CH), 1647 (NH_2), 1014 cm^{-1} (furazan).

3-(4-Methoxymethyleneaminofurazan-3-yl)-1,2,4-oxadiazole (III, $C_6H_5N_5O_3$) and 3-(4-Formamidofurazan-3-yl)-1,2,4-oxadiazole (IV, $C_5H_3N_5O_3$). A suspension of 0.29 g (2 mmoles) of amidoxime I in 3 ml trimethylorthoformate is treated with 0.01 g boron trifluoride etherate and refluxed for 5 h. The reaction mixture is evaporated in vacuum and the residue chromatographed on silica gel (eluent ether–hexane, 1:1). Yield 0.20 g (51%) of iminoester III and 0.08 (22%) of formyl derivative IV.

Compound III, mp 71-73°C. PMR spectrum: 3.89 (3H, s, CH_3), 8.43 (1H, s, CH), 9.89 ppm (1H, s, ring CH). IR spectrum: 3140 (ring CH), 1640 cm^{-1} (C=N).

Compound IV, mp 131-133°C. PMR spectrum: 8.52 (1H, s, CH), 9.97 (1H, s, ring CH), 10.9 ppm (1H, s, NH). IR spectrum: 3337 (NH), 3140 (ring CH), 1770 cm^{-1} (C=O).

4-Dimethylaminomethyleneaminofurazan-3-carboxyamideoxime (V, $C_6H_{10}N_6O_2$). A suspension of 1.43 g (10 mmoles) of amidoxime I in 2.38 g (20 mmoles) of dimethylformamide dimethylacetal is stirred for 30 min at room temperature. The reaction mixture is diluted with ether and the deposit filtered off. Yield 1.22 g (62%) of compound VIII with mp 192-194°C (from ethanol). PMR spectrum: 2.89 and 3.00 (3H, s, and s, $(CH_3)_2N$), 5.97 (2H, s, NH_2), 8.16 (1H, s, CH), 10.2 ppm (1H, s, OH). IR spectrum: 3510 and 3300 (NH_2), 3200 (OH), 1670 (C=N), 1638 cm^{-1} (NH_2).

3-(4-Dimethylaminomethyleneaminofurazan-3-yl)-1,2,4-oxadiazole (IV, $C_7H_8N_6O_2$). A. A solution of 1.43 g (10 mmoles) of amidoxime I in 10 ml dimethylformamide is treated with stirring with 3.07 g (20 mmoles) phosphorus oxychloride. The temperature rises to 100°C. After 10 min the reaction mixture is cooled and poured into 50 ml water, neutralized with a concentrated soda solution, and the precipitate formed filtered off. Yield 1.5 g (72%) oxadiazole VI.

B. A solution of 1.00 g (5 mmoles) of amidoxime V in 3.0 ml orthoformyl ester and 0.02 g boron trifluoride etherate is refluxed for 5 min and cooled. The reaction mixture is diluted with ether and the precipitate filtered off. Yield 0.85 g (82%)

of compound VI; mp 130-131°C (from ethanol). PMR spectrum: 3.00 and 3.10 (3H, s, s, $(CH_3)_2N$), 8.37 (1H, s, CH), 10.0 ppm (1H, s, ring CH). IR spectrum: 3140 (ring CH), 1633 (C=N), 1017 cm^{-1} (furazan).

4-(1-Ethoxyethylideneamino)furazan-3-carboxyamidoxime (VII, $C_7H_{11}N_5O_3$). A suspension of 0.29 g (2 mmoles) of amidoxime I in 3 ml triethylorthoformate is treated with 0.01 g boron trifluoride etherate, stirred until dissolution of the precipitate is complete, and kept for 5 h at room temperature. The reaction mixture is evacuated in vacuum without heating and the residue chromatographed on silica gel (eluent ether–hexane 1:1). Yield 0.24 g (56%) of iminoester VII; mp 110-112°C. PMR spectrum: 1.22 (3H, t, J = 7 Hz, $\underline{CH_3}CH_2$), 1.83 (3H, s, CH_3), 4.16 (2H, q, J = 7 Hz, $CH_3\underline{CH_2}$), 5.92 (2H, s, NH_2), 10.2 ppm (1H, s, OH). IR spectrum: 3430 and 3330 (NH_2), 3200 (OH), 1675 (C=N), 1640 cm^{-1} (NH_2).

5-Methyl-3-[4-(1-ethoxyethylideneamino)furazan-3-yl]-1,2,4-oxadiazole (VIII, $C_9H_{11}N_5O_3$). A suspension of 0.29 g (2 mmoles) of amidoxime I in 3 ml triethylorthoformate is treated with 0.01 g boron trifluoride, stirred until dissolution of the precipitate is complete, and kept for 24 h at room temperature. The reaction mixture is evaporated in vacuum and the residue chromatographed on silica gel (eluent ether–hexane 1:3). Yield 0.28 g (60%) of iminoester VIII; mp 44-46°C. PMR spectrum: 1.22 (3H, t, J = 7 Hz, $\underline{CH_3}CH_2$), 1.90 (3H, s, CH_3), 2.60 (3H, s, 5-CH_3), 4.21 ppm (2H, q, J = 7 Hz, $CH_3\underline{CH_2}$). IR spectrum: 1660 cm^{-1} (C=N).

7-Oximino-5-ethoxycarbonyl-6,7-dihydrofurazano[3,4-d]pyrimidine (X, $C_7H_7N_5O_4$). A mixture of 0.43 g (3 mmoles) of amidoxime I and 2.0 g (9 mmoles) of ethyl ester of triethoxyacetic acid is heated for 15 min at 110-120°C. The reaction mixture is cooled, diluted with 10 ml ether, and the precipitate filtered off. Yield 0.23 g (34%) of compound X with T_{subl} 240°C. PMR spectrum: 1.29 (3H, t, J = 7 Hz, CH_3), 4.30 (2H, q, J = 7 Hz, CH_2), 10.8 (1H, s, OH), 12.0 ppm (1H, s, NH). IR spectrum: 3360 (OH), 3120 (NH), 1745 (C=O), 1650 cm^{-1} (C=N).

4-Aminofurazan-3-carboxyamid-O-acetyloxime (XI, $C_5H_7N_5O_3$). A suspension of 4.29 g (30 mmoles) of amidoxime I in 25 ml acetic anhydride is stirred for 2 h at room temperature. Water (60 ml) is added, the mixture stirred for 20 min, and the precipitate filtered off. Yield 5.0 g (90%) of compound XI with mp 201-202°C (from ethanol–water, 1:1). PMR spectrum: 2.11 (3H, s, CH_3), 6.31 (2H, s, NH_2), 7.22 ppm (2H, s, NH_2). IR spectrum: 3419, 3400, 3320, and 3204 (NH_2), 1766 (C=O), 1655 (NH_2), 1008 cm^{-1} (furazan).

4-Acetamidofurazan-3-carboxyamide-O-acetyloxime (XII, $C_7H_9N_5O_4$). A solution of 2.78 g (15 mmoles) of amidoxime I in 12 ml acetic anhydride is refluxed or 3 h. The mixture is cooled to room temperature, diluted with ether, and the precipitate filtered off. Yield 2.75 g (78%) of compound XII, mp 191-193°C (from ethanol–water 1:1). PMR spectrum: 2.11 (3H, s, CH_3), 2.13 (3H, s, CH_3), 7.49 (2H, s, NH_2), 10.3 ppm (1H, s, NH). IR spectrum: 3460 b 3318 (NH_2), 3261 (NH), 1789 (C=O), 1723 (C=O), 1670 (NH_2), 1015 cm^{-1} (furazan).

4-Trifluoroacetamidofurazan-3-carboxyamido-O-trifluoroacetyloxime (XIII, $C_7H_3F_6N_5O_4$). Amidoxime (1 g, 7 mmoles) is dissolved at room temperature in 8 ml trifluoroacetic anhydride. The precipitate is filtered off after 10 min. Yield 1.64 g (70%) of compound XIII, mp 132-134°C (from chloroform).IR spectrum: 3445 and 3350 (NH_2), 3285 (NH), 1810 (C=O), 1769 (C=O), 1655 (NH_2), 1130-1250 cm^{-1} (CF_3).

3-(4-Aminofurazan-3-yl)-5-trifluoromethyl-1,2,4-oxadiazole (XVII, $C_5H_2F_3N_5O_2$). A solution of 1.0 g (3 mmoles) of the trifluoroacetyl derivative XIX in 10 ml toluene is refluxed for 3 h. The toluene is stripped off in vacuum, the residue is treated with toluene and the precipitate filtered off. Yield 0.42 g (63%) of compound XVII, mp 126-128°C, (from 2-propanol). PMR spectrum: 6.51 ppm (2H, s, NH_2). IR spectrum: 3478 and 3325 (NH_2), 1150-1240 cm^{-1} (CF_3).

3-(4-Aminofurazan-3-yl)-5-trichloromethyl-1,2,4- oxadiazole (XVIII, $C_5H_2Cl_3N_5O_2$). Trichloroacetyl chloride (5.46 g, 30 mmoles) is treated in portions with 1.43 g (10 mmoles) of amidoxime I at 60-80°C. The mixture is heated 15 min at 110-115, cooled, and poured into 20 ml saturated sodium bicarbonate solution. The precipitate is filtered off. Yield 1.57 g (58%) of compound XVIII, mp 114-116°C. PMR spectrum: 6.49 ppm (2H, s, NH_2). IR spectrum: 3441 and 3320 (NH_2), 1638 (NH_2), 1020 cm^{-1} (furazan).

7-Acetoxyimino-6,7-dihydrofurazano[3,4-d]pyrimidine (XIX, $C_6H_5N_5O_3$). A suspension of 1.85 g (10 mmoles) of the acetamidoxime XI in 10 ml triethylorthoformate and 0.02 g boron trifluoride etherate was heated 10 min at 70-80°C; the reaction mixture was cooled and the precipitate formed filtered off. Yield 1.4 g (72%) of furazanopyrimidine XIX, mp 218-220°C (from ethanol). PMR spectrum: 2.16 (3H, s, CH_3), 7.84 (1H, s, CH), 12.1 ppm (1H, s, NH). IR spectrum: 3260 (NH), 3090 (ring CH), 1763 (C=O), 1024 cm^{-1} (furazan).

7-Hydroxyimino-6-phenyl-6,7-dihydrofurazano[3,4-d]pyrimidine (XXI, $C_6H_5N_5O_3$). A solution of 1.10 g (5 mmoles) 4-aminofurazan-3-carboxy-N-phenylamidoxime XX and 0.02 g boron trifluoride etherate in 5 ml triethylorthoformate was kept 48 h at room temperature and the precipitate filtered off. Yield 0.63 g (55%) of the furazanopyrimidine XXI, mp 215-217°C (from ethanol). PMR spectrum: 7.51 (5H, s, Ph), 7.93 (1H, s, CH), 11.7 ppm (1H, s, OH).

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2. T. Ichikawa, T. Kato, and T. Takenishi, J. Heterocycl. Chem., **2**, 253 (1965).