Ring Transformation with Bridged 1,3-Dicarbonyl Heteroanalogues, III[1]:

5-(ω-Aminoalkyl)-1,2,4-oxadiazoles by Ring-Transformations of 3-Methylthio-2-aza-3-propeniminium Salts

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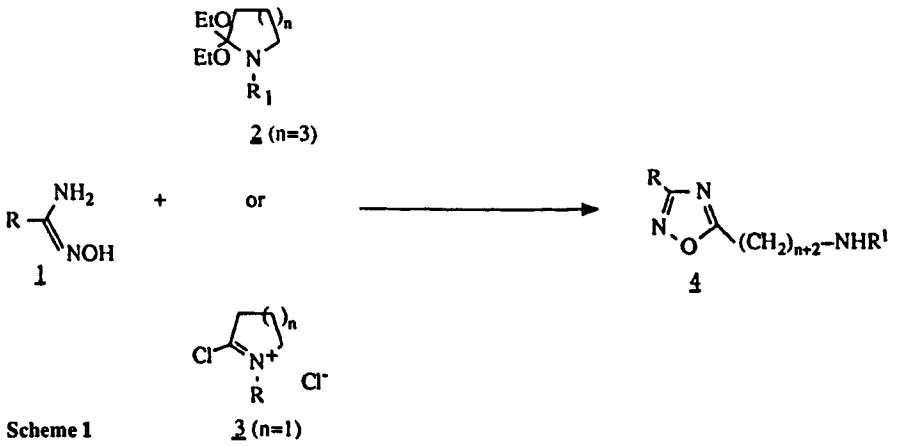
Received September 18, 1989

3-Methylthio-2-aza-3-propeniminium salts **5** react with hydroxylamine after ring transformation under formation of 5-(ω-aminoalkyl)-1,2,4-oxadiazole hydroiodides **4**·HI, which show a remarkable antitussive activity.

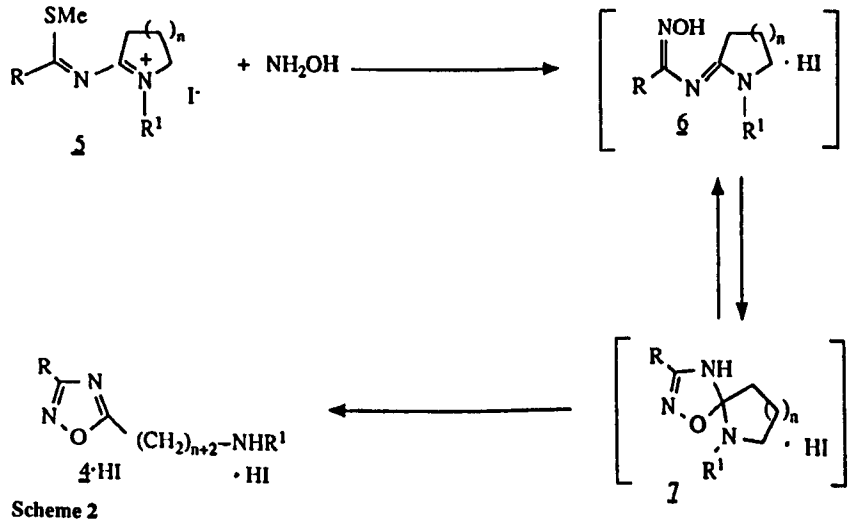
Ringtransformationen an verbrückten 1,3-Dicarbonyl-heteroanalogen, 3. Mitt.: 5-(ω-Aminoalkyl)-1,2,4-oxadiazole durch Ringtransformation von 3-Methylthio-2-aza-3-propeniminiumsalzen

3-Methylthio-2-aza-3-propeniminiumsalze **5** reagieren mit Hydroxylamin nach einer Ringtransformation unter Bildung von 5-(ω-Aminoalkyl)-1,2,4-oxadiazol Hydroiodiden den **4**·HI. Diese zeigen eine auffällige antitussive Wirkung.



Scheme 1

A number of ω-aminoalkylheteroaromatics, *i.e.* 3-(β-aminoethyl)-imidazole (histidine)[2], 5-(β-diethylaminoethyl)-3-phenyl-1,2,4-oxadiazole (oxolamine)[3], and 5-(ω-aryloxyalkyl)-isoxazoles[4] exhibit interesting pharmacological properties. Various synthetic routes have been followed to produce these specific compounds. 5-(ω-Aminopropyl)- and 5-(ω-aminopentyl)-1,2,4-oxadiazoles **4** (R = phenyl, benzyl, ethyl; R^1 = methyl; n = 1,3) were synthesized by reaction of amidoximes **1** as a N-C-N-O synthon with a lactam acetal **2** or a cyclic amide chloride **3** acting as C synthon[5]. Analogously the application of lactim ethers leads to alkyl-1,2,4-oxadiazoles **4** with an unsubstituted amino group in ω-position[5]. In this type of ring transformation the lactam ring is opened producing the aminoalkyl chain while the oxadiazole ring is formed.



Scheme 2

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Table 1: 5-(ω-Aminoalkyl)-1,2,4-oxadiazol-hydroiodides 4·HI

Nr.	R	R^1	n	mp. (°C) yield	^{1}H-NMR (DMSO) (δ in ppm)	MS (rel.Int. in %)
4a*; **	4-MeO-Ph	Me	1	158-160 78	2.2(m, 2H)CH_2; 2.6(s, 3H)NMe; 3.1(m, 4H)2·CH_2; 3.8(s, 3H)OMe; 7.0(d, J=9 Hz, 2H); 7.8(d, J=9 Hz, 2H); 8.3(br., 1H)NH	
4b	4-Cl-Ph	Me	1	180-181 65	2.4(m, 2H)CH_2; 2.9(s, 3H)NMe; 3.5(m, 4H)2·CH_2; 6.8(br., 1H)NH; 7.8(d, J=9 Hz, 2H); 8.1(d, J=9 Hz, 2H)	252(M^+, 10); 156(17); 137(23); 113(11); 98(11); 75(49); 44(100)
4c	-NH-Ph	Me	1	180-182 68	2.4(m, 2H)CH_2; 2.8(s, 3H)NMe; 3.4(m, 4H)2·CH_2; 7.4(s, 5H)Ph; 8.7(s, 1H)NH; 10.1(s, 1H)NH	232(M^+, 10); 175(17); 133(14); 128(14); 98(16); 77(13); 58(25); 44(100)
4d	-NH_2	Me	1	183-185 53	2.4(m, 2H)CH_2; 3.0(s, 3H)NMe; 3.3(m, 4H)2·CH_2; 6.5(s, 2H)NH_2	156(M^+, 1); 128(10); 99(12); 58(12); 44(100)
4e	thien-2-yl	Me	1	204-205 64	2.1(q, J=7 Hz, 2H)CH_2; 2.6(s, 3H)NMe; 3.0(t, J=7 Hz, 2H)CH_2; 3.1(t, J=7 Hz, 2H)CH_2; 7.2(t, J=4 Hz, 2H); 7.8(d, J=4 Hz, 1H); 7.9(d, J=4 Hz, 1H)	223(M^+, 1); 128(19); 58(19); 44(100)
4f	4-Me_2N-Ph	Et	2	174-175 92	1.2(t, J=7 Hz, 3H)Me; 1.7(m, 4H)2·CH_2; 2.9-3.1(m, 8H)CH_2, NMe_2; 6.7(d, J=9 Hz, 2H); 7.7(d, J=9 Hz, 2H); 7.8(br., 1H)NH	288(M^+, 4); 203(10); 164(13); 16(23); 127(17); 98(25); 84(26); 71(43); 58(100)
4g	4-Cl-Ph	Me	3	157-158 87	1.5(m, 6H)3·CH_2; 2.3(s, 3H)NMe; 2.9(m, 4H)2·CH_2; 7.6(s, J=8 Hz, 2H); 7.9(d, J=8 Hz, 2H)	

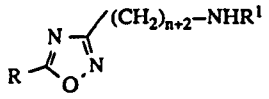
* ^{13}C-NMR (DMSO) δ in ppm: 22.1; 22.9; 32.5; 47.2; 55.4; 114.5; 118.4; 128.5; 161.5; 167.1; 178.7

** Pharmacological test: citric acid induced gough (guinea pig): ED_{50} = 75.5 (40.3 - 129.8) mg/kg
letal dose (mouse): LD_{50} = 1000 mg/kg

We became interested to synthesize 5-(ω-aminoalkyl)-1,2,4-oxadiazoles 4 in a wider scope by employing another type of ring transformation that avoids amidoximes **1**. As we could show recently, readily available[6,7] 3-methylthio-2-aza-3-propeniminium salts **5** react as 1,3-bifunctional electrophiles with hydrazines in position 1 and 3 giving a ring transformation to ω-aminoalkyl-1,2,4-triazoles[6,7].

Consequently the application of hydroxylamine instead of hydrazines as bifunctional nucleophile should lead to ω-aminoalkyl-1,2,4-oxadiazoles **4**. While hydroxylamine hydrochloride solution did not work, free hydroxylamine gives smooth reactions with 3-methylthio-2-aza-3-propeniminium salts **5**. Products isolated in satisfactory to high yields are the 5-(ω-aminoalkyl)-1,2,4-oxadiazoles **4** which precipitate as hydroiodides 4·HI (Table 1)[7,8]. Intermediates such as condensation products **6** or spiro compounds **7**, which can also be considered tautomers of **4**, were not obtained.

5-(ω-Aminoalkyl)-1,2,4-oxadiazole hydroiodides 4·HI have been unknown so far. Their structures can be proved by elemental analysis and in particular by spectroscopic methods (Table 1). ^{1}H-NMR-spectra exhibit the characteristic pattern of chemical shifts of the alkyl chain protons of ω-functionalized heteroaromatics[1,6,7,9]: δ N-CH_2-C > δ CH_2-oxadiazole > δ C-$(CH_2)_n$-C differ significantly from those found in spiro intermediates similar to **7**, or in lactamimine derivatives[1,6,7,9] such as **6**. In addition intensive peaks of 44 ($CH_3NHCH_2^+$-onium cleavage), 58 (CH_3NH-CH_2-CH_2^+) and M^+-57 (*McLafferty* rearrangement) are found in the MS which are typical of ω-aminoalkyl heteroaromatic compounds[1,6,7]. Results of MS also rule out isomeric 3-(ω-aminoalkyl)-1,2,4-oxadiazole structures **8** since fragmentation is analogous to known 5-alkyl-3-aryl-1,2,4-oxadiazoles[12], *i.e.* fragment peaks of RCN_2 are found, which are characteristic for 5-alkyl-3-aryl-1,2,4-oxadiazoles but do not fit to isomers **8**[12]. Furthermore in analogy to 1,2-oxazole derivatives[13] isomers **8** can be expected to give fragment peaks of RCO, which are missing in the mass spectra of the compounds obtained.



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Scheme 3

Additional evidence for structure **4** is given by ^{13}C-NMR-spectra. Chemical shifts of C-atoms 3 and 5 of the oxadiazole ring 4a·HI are found at 167.7 and 178.7 ppm, respectively, which closely correspond to other known 5-alkyl-3-aryl-1,2,4-oxadiazoles[12].

It is worth mentioning that in the reaction of non-bridged *N*-acyl-thioamides with hydroxylamine an analogous orientation of reactands is found[10].

Pharmacological testing of compound 4a·HI revealed that its antitussive activity is similar to that of the commercial antitussivum Oxolamine®.

Transformation of 3-methylthio-2-aza-3-propeniminium iodides **5** to 5-(ω)-1,2,4-oxadiazole hydroiodides 4·HI represents an efficient method to synthesize these compounds with a wider variability of substituents compared to the known route to the free bases **4**[5]. In particular 3-anilino substituted compounds 4·HI (R = anilino) become available.

Furthermore these results once again demonstrate the wide scope of the ring transformation principle (see[6] and ref. cited there) transforming bridged 1,3-dicarbonyl heteroanalogues to ω-functionalized heteroaromatic compounds.

Experimental Part

Hydroxylamine solution

35 g (0.5 mol) of hydroxylamine hydrochloride are dissolved in about 200 ml of boiling methanol. A solution of 12.5 g (0.5 mol) sodium in 250 ml methanol is added. The resultant solution is filtered while still hot. Methanol is added to the filtrate up to a total volume of 500 ml.

5-(ω-Aminoalkyl)-1,2,4-oxadiazole Hydroiodides 4·HI

0.01 mol of the 3-methylthio-2-aza-3-propeniminium iodide 5[6], prepared from the corresponding semicyclic N-thioacylamidine[11] and CH_3I, are added to 15 ml of freshly prepared methanolic solution of hydroxylamine (see above). The mixture is refluxed for 30 min. Product 4·HI precipitates during cooling to room temp. It is filtered by suction and recrystallized from ethanol.

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