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1,2,5−Oxadiazoles Substituted at Ring Nitrogen. Part 1. Synthesis and Study of 2−Ethyl−1,2,5−oxadiazol−3(2H)−ones[1].

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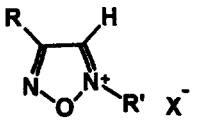
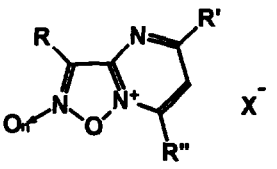
Abstract. The first representatives of the 2−alkyl−1,2,5−oxadiazol−3(2H)−ones have been synthesized by the alkylation of trimethylsilyl derivatives of 3−hydroxyfurazans using triethyl orthoformate. The compounds obtained are investigated by ^{13}C,^{14}N,^{15}N and ^{17}O NMR, MS, IR and UV.

INTRODUCTION

Derivatives with substituents at ring nitrogen are rather rare for the 1,2,5−oxadiazole (furazan) system. Isolated reliable examples of such substances are scattered in the literature. Thus, for a long time the only known compounds of this type were quaternized derivatives I.[2]

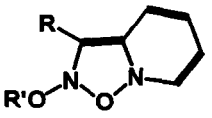


I

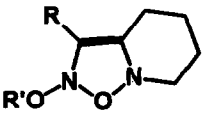


II

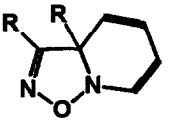
Bicyclic salts of type II were obtained later.[3] Neutral bicyclic compounds of types III[4a], IV[4a] and V[4b] with bridge−head nitrogen have also been reported, as have the bicyclic compounds VI[5],



III

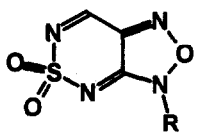


IV



V

containing a 1,2,5–oxadiazoline ring with 3,4–ring fusion.



VI

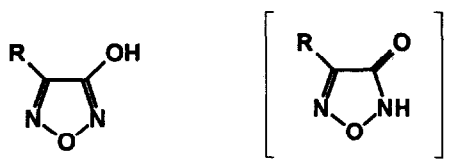
Other examples of N–substituted 1,2,5–oxadiazoline structures[6,8,10] proved to be unfounded; further investigation showed the compounds to have different structures.[7,9,11]

Synthesis and porperties of various compounds including an N–substituted furazan moiety attracted our attention.

RESULTS AND DISCUSSION

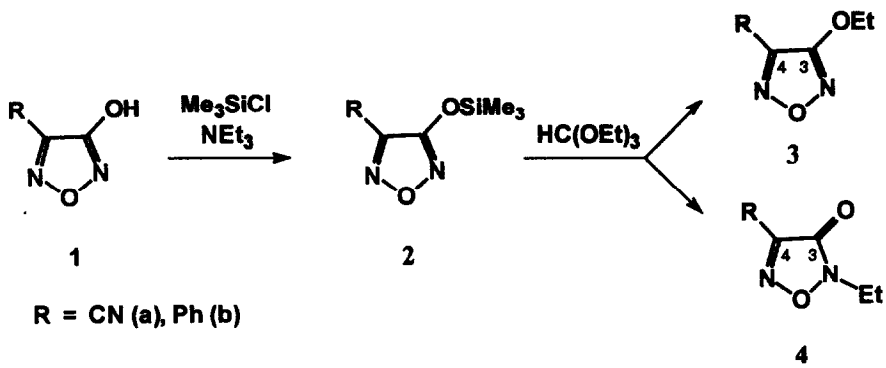
The present study is concerned with the synthesis of uncondensed N–substituted derivatives of 1,2,5–oxadiazol–3(2H)–one (1,2,5–oxadiazolin–3–one).

The 1,2,5–oxadiazole (furazan) ring is a stable system, not significantly subject to annular–group tautomerism; the hydroxy form is in practise not involved in equilibrium with the carbonyl form.[12]



For the same reason this system is not N–alkylated by the usual methods, in contrast to the other oxadiazoles, which produce mixtures of N– and O–substituted derivatives.[12] The silyl method appeared to offer some prospect for a successful N–alkylation in the furazan ring, because hydroxy or potential hydroxy derivatives of other nitrogen heterocycles, when alkylated by this method, gave mainly N–substituted products.[13]

Treatment of **1** with trimethylchlorosilane (TMCS) in the presence of triethylamine (TEA) gave the corresponding silyl derivatives **2** in practically quantitative yield, as determined by NMR spectroscopy. The derivatives **2** were used directly in the further transformations without additional purification.



1 2 3 4

R = CN (a), Ph (b)

Reaction of **2** with ethyl orthoformate at 160–180°C led to two types of product, **3** and **4**, in comparable quantities. Both substances showed the same elemental composition, but different physico–chemical and spectral characteristics.

Reaction of **1** with orthoester under the above conditions proceeded with extensive decomposition, and gave only product **3** in low yield along with some **1** recovered.

In contrast to **3**, the IR–spectra of compound **4** contained a strong carbonyl absorption band at ~1700 cm^{-1}. The UV–spectra showed absorption at ~260 and ~290 nm, for **3** and **4** respectively. Compound **3b** (R=Ph) turned out to be identical to the known 3–phenyl–4–ethoxyfurazan.[14] The furazan structure was accordingly assigned to **3a** (R=CN).

The second type of reaction products could have the desired 1,2,5–oxadiazolin–3–one structure **4**. However, since furazans are known to undergo rearrangement at high temperature to the corresponding 1,2,4–oxadiazole derivatives,[15] the structures **5** and **6**, with the same elemental composition and similar IR– and UV–spectra, could not be excluded from consideration.

5 6

We therefore measured the direct ^{1}J (^{13}C–^{13}C) NMR coupling constants (Table 1) by means of an INADEQATE experiment.[16] The values show the carbon atoms C3 and C4 to be separated by one bond both in the compounds **3**[17] and **4**; thus, 1,2,4–oxadiazol(in)e structures can be ruled out.

Tables 2 and 3 present ^{13}C, ^{14}N, ^{15}N, ^{17}O, ^{29}Si NMR data for all compounds obtained.

Table 1. ^{1}J ($^{13}C - ^{13}C$) coupling constants of compounds **3b** and **4b**

Bond	Compounds	
$C_X - C_Y$	**3b**	**4b**
C3 – C4	63.4	62.3
C4 – C_i	67.4	67.2
$C_i - C_o$	58.4	58.2
$C_o - C_m$	56.8	57.0
$C_m - C_p$	55.3	55.4

Table 2. ^{13}C NMR Data of Compounds **1,2,3** and **4.**

Compounds	^{13}C				
	C3	C4	CH_2	CH_3	R
1a	164.62	127.69	–	–	107.90(C≡N)
2a[a]	160.95	126.75	–	−1.61	105.41(C≡N)
3a	166.07	127.55	71.44	14.60	107.67(C≡N)
4a	153.70	135.52	43.28	13.02	108.32(C≡N)
1b	162.85	146.34	–	–	i 126.57 o 128.18 m 129.93 (Ph) p 131.47
2b[b]	160.24	145.88	–	−0.84	i 125.24 o 126.87 m 128.54 (Ph) p 130.13
3b	163.48	145.15	68.71	14.50	i 125.31 o 127.40 m 128.86 (Ph) p 130.52
4b	155.23	149.54	40.84	12.84	i 125.53 o 126.92 m 128.78 (Ph) p 131.16

[a] δ (^{29}Si) = 31.40 ppm

[b] δ (^{29}Si) = 38.10 ppm

The structures **3** and **4** can be distinguished easily by the chemical shifts of the $^{13}CH_2$ in the ethyl group. Signals from $O-CH_2$ are considerably shifted to lower field ($\delta \sim 70$ p.p.m.) in comparison with the $N-CH_2$ signals ($\delta \sim 40$ p.p.m.), due to the increased electronegativity of the oxygen atom. Similarly, the shift of the CH_2 groups in the ^1H–NMR spectra differ (see Experimental).

Using the SPT method,[18] we managed to measure ^2J ($^1H_2C-^{15}N$) (0.8 Hz) for **4b**; in **3b** the $^1H-^{15}N$ coupling constant through four bonds was not observed.

The ^{15}N signal in **4** appears considerably up–field when compared with the usual signals of furazan nitrogen atoms (20–45 p.p.m.[17b]). Considerable differences in ^{17}O shifts of both endocyclic and exocyclic oxygen atoms are apparent when **4** is compared with furazan structures.

Table 3. ^{17}O, ^{14}N and ^{15}N NMR Data.

Compounds	^{17}O		^{14}N	^{15}N
	endocyclic	exocyclic		
1a	–	–	55; −6; −102 (C≡N)	–
2a	422	64	–	–
4a	324	230	*	**
4b	306	234	*	−141,9

* – very broad lines.

** – not observed.

Compounds **3** and **4** show different fragmentation patterns under electron impact (EI). The mass–spectra of O– and N–alkylated compounds are shown in Figs. 1 and 2. These compounds both have very stable $M^{+\cdot}$ ions. Ethoxyfurazans under EI undergo two types of fragmentation. On the one hand the compounds are similar to ethoxybenzenes,[19a] undergoing an H–1 type of rearrangement with elimination of ethylene. Alternatively, an NO molecule can be eliminated, which is typical of furazan derivatives.[19b]

The fragmentation of 1,2,5–oxadiazolines **4** proceeds in quite a different manner. The fragment ions $C_2H_5NCO^{+\cdot}$, $C_2H_5NO^{+\cdot}$, $PhCN^{+\cdot}$ and the corresponding ions from $M^{+\cdot}$ with elimination of these (neutral) fragments can be considered as typical of the mass spectra of these compounds. The fragmentation also provides evidence that the ethyl substituent is bonded to the ring nitrogen.

A contributory dipolar structure **7** can be considered in addition to the amide formula **4**.

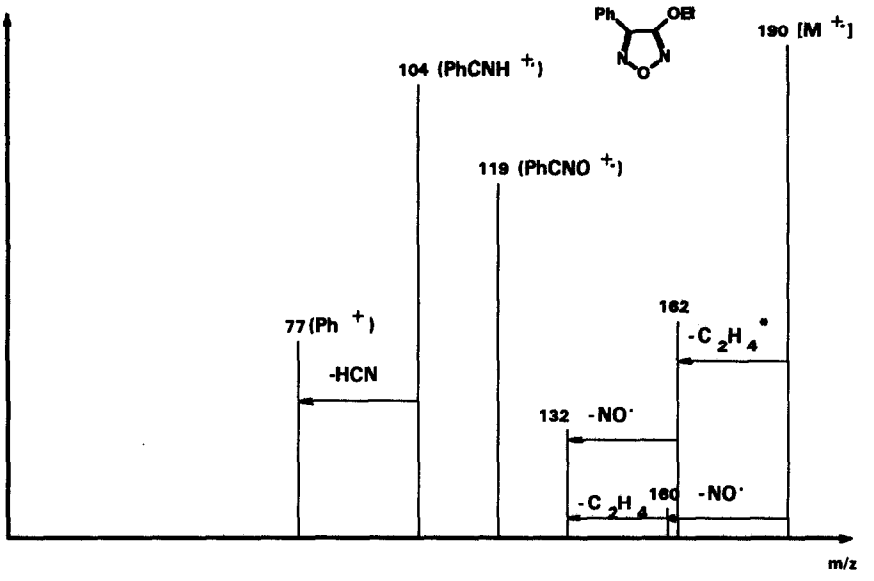


Fig.1. Mass spectrum of **3b**.

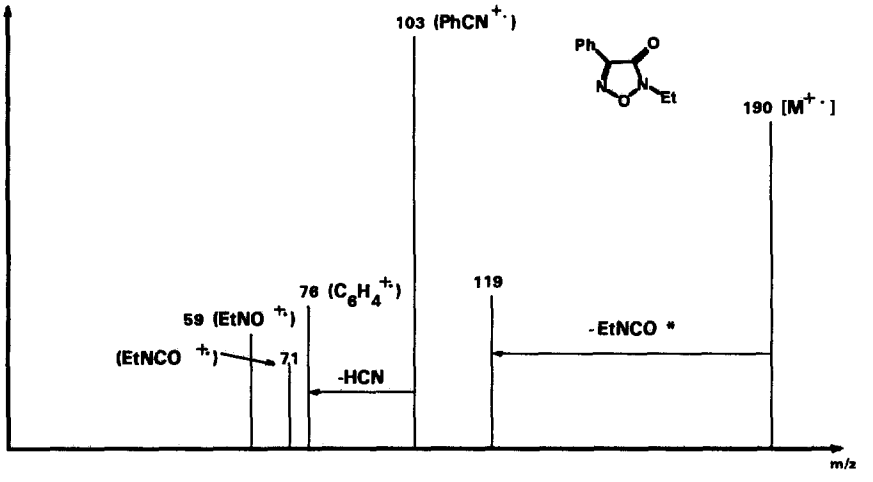
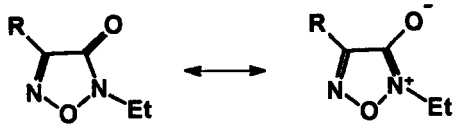


Fig.2. Mass spectrum of **4b**.

The contribution of these canonical forms to the real structure of the compound can be estimated using the chemical shifts of the ^{17}O NMR signals. The exocyclic oxygen atoms in the structures **4** and **7** are essentially different: in **4** it is close to the oxygen of an amide group



4 **7**

(in which δ of ^{17}O is 275–313 ppm[20]), whereas in **7** it is similar to that in the hydroxyfurazan anion (e.g., δ ^{17}O in the pyridinium salt of 3–hydroxy–4–phenylfurazan is 65 ppm, as we find). The exocyclic oxygen signal in the N–alkylated compound appears at ~230 ppm. We conclude that structure **4** is the principal contributor and may be used quite adequately to depict the real structure of this compound.

In conclusion, we have obtained for the first time uncondensed products of N–substitution in 1,2,5–oxadiazoles with a functional group in the ring, the 2–ethyl–1,2,5–oxadiazol–3(2H)–ones.

EXPERIMENTAL

IR spectra were determined in KBr pellets on a UR–20 spectrophotometer. Mass–spectra were recorded on a Varian CH–6 instrument. UV spectra were taken in MeOH on a Beckman DU–7 spectrophotometer. ^{1}H, ^{13}C, ^{14}N, ^{15}N and ^{17}O NMR spectra were registered on a Bruker AM–300 spectrometer at 300.13, 75.5, 21.5 and 40.7 MHz. Chemical shifts were measured relative to internal reference TMS (^{13}C and ^{1}H), external CH_3NO_2 (^{14}N, ^{15}N) and external H_2O (^{17}O). TLC was carried out on Silufol F_{254}.

3–Hydroxy–4–cyanofurazan, **1a**. A solution of 3–hydroxyfurazancarboxamide[21] (1.29 g, 10 mmol) and DMF (0.7 g, 10 mmol) in 15 mL of thionyl chloride was warmed to 40°C and stirred for 5h. The mixture was poured into ice and extracted with Et_2O (2 × 50 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated to afford a yellow oil which was purified by distillation (8 mmHg, 123°C) to give 0.63 g (56%) of **1a** as a colorless oil which quickly crystallized in the receiver: mp. 37–40°C; **IR** ν: 3600–3000, 2275, 1595, 1440, 1330, 1255, 1230, 1030 cm^{-1}; **MS**: m/z 111 [M^+].

3–Hydroxy–4–phenylfurazan, **1b**. To a solution of 3–nitro–4–phenylfurazan[22] (1.21 g, 10 mmol) in 8 mL of glyme was added dropwise a solution of NaOH (0.8 g, 20 mmol) in 5 mL

of water with vigorous stirring. The stirring was continued for 2h at 70°C. The mixture was cooled, diluted with water (50 mL), and purified by extraction with $CHCl_3$ (30 mL). The aqueous layer was acidified (HCl) and extracted with Et_2O (3 × 50 mL). The combined extracts were dried ($MgSO_4$), filtered, and evaporated. The residue was precipitated from acetone by water, to give **1b** (1.4 g, 86%) as white prisms: mp. 177.5–178°C; **IR** ν: 3300–2850, 2670, 2600, 2500, 1580, 1555, 1535, 1465, 1310, 1250, 1050, 970, 870 cm^{-1}; **MS**: m/z 162 [$M^{+\cdot}$].

General Procedure. Under an argon or nitrogen atmosphere, TMCS (5mL) was added to a solution of **1** (10 mmol) and TEA (1.01 g, 10 mmol) in $CHCl_3$ (15 mL). The mixture was stirred 8h, diluted with diethyl ether (25 mL) and the precipitate was filtered off. Evaporation of the filtrate under reduced pressure afforded **2** as an oil. Triethyl orthoformate (1.83 g, 10 mmol) was added to the oil and the resulting mixture was heated on an oil bath at 180–200°C for 5 min. After cooling the mixture was purified by column chromatography to give **3** and **4**.

3–Cyano–4–ethoxyfurazan, **3a**, 46%, mp. –30°C, bp. 173°C, R_f = 0.9 (CH_2Cl_2); **IR** ν: 3013, 2285, 1600, 1520, 1495, 1405, 1270, 1245, 1050, 1040, 910, 890 cm^{-1}; **MS**: m/z (%) 139 ($M^{+\cdot}$, 87), 111 ($M^{+\cdot} - C_2H_4$, 25), 109 ($M^{+\cdot} - NO\cdot$, 10), 81 ($M^{+\cdot} - C_2H_4 - NO\cdot$, 100); **UV**: 254; ^{1}**H NMR** (acetone – d_6) δ 4.58 (q, 2H), 1.53 (t, 3H) ppm.

4–Cyano–2–ethyl–1,2,5–oxadiazol–3(2H)–one, **4a**, 41%, mp. 12°C, bp. 235°C, R_f = 0.3 (CH_2Cl_2); **IR** ν: 3005, 2970, 2270, 1720, 1535, 1460, 1395, 1270, 1175, 1100, 1015 cm^{-1}; **MS**: m/z (%) 139 ($M^{+\cdot}$, 100), 59 ($EtNO^{+\cdot}$, 63); **UV** 291; ^{1}**H NMR** (acetone – d_6) δ 4.65 (q, 2H), 1.46 (t, 3H) ppm.

3–Ethoxy–4–phenylfurazan, **3b**, 29%, mp. 62–63°C, R_f = 0.9 (CH_2Cl_2); **IR** ν: 2995, 1600, 1575, 1540, 1480, 1395, 1370, 1330, 1300, 1290, 1170, 1140, 1100, 880 cm^{-1}; **UV** 258; ^{1}**H NMR** ($CDCl_3$) δ 8.01 (d, 2H), 7.50 (m, 3H), 4.52 (q, 2H), 1.55 (t, 3H) ppm.

2–Ethyl–4–phenyl–1,2,5–oxadiazol–3(2H)–one, **4b**, 20%, oil, R_f = 0.48 (CH_2Cl_2); **IR** ν: 3075, 3000, 2950, 1700, 1680, 1500, 1460, 1360, 1285, 1175, 980, 950 cm^{-1}; **UV** 284; ^{1}**H NMR** ($CDCl_3$) δ 8.26 (d, 2H), 7.50 (m, 3H), 4.17 (q, 2H), 1.45 (t, 3H) ppm.

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