5-HYDROXY-1,3-OXAZIN-6(6*H*)-ONES FROM 6-AZA-1,5-DIOXA-SPIRO [2.4]HEPT-6-EN-4-ONES

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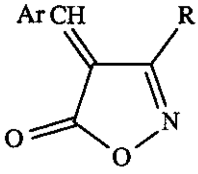
Abstract - 4-Alkylideneisoxazol-5(4*H*)-ones (**1**) were epoxidized with *t*-butyl hydroperoxide yielding 6-aza-1,5-dioxaspiro[2.4]hept-6-en-4-ones (**2**). By heating, compounds (**2**) rearranged to 5-hydroxy-1,3-oxazin-6(6*H*)-ones (**3**).

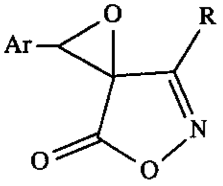
Previous work from our research group dealt with the reactions of substituted 4-methylene-*v*-triazolines and 4-methyleneisoxazolines[1] with peroxy acids. The reaction gives a practical entry to 1-aryl-*v*-triazole-4-carboxaldehydes and 3-arylisoxazole-4-carboxaldehydes, respectively. As reaction intermediates spiranic compounds containing both oxirane and heterocyclic rings were postulated.

As a further contribution to the chemistry of the scarcely known spiranic oxiranes derived from alkylidene heterocycles, we now report our results on the condensation and rearrangement reaction of substituted 6-aza-1,5-dioxaspiro[2.4]hept-6-en-4-ones (**2**).

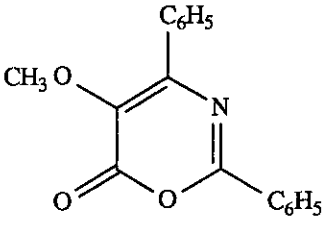
The 4-alkylideneisoxazol-5(4*H*)-ones (**1**) (except **1c**) are known compounds and were obtained by means of described procedures.[2-4] The epoxidation reaction could not be performed with peroxy acids in acidic medium because of the too low reactivities of **1** . Instead, satisfactory results were obtained by basic epoxidation. The best results were offered by *t*-butyl hydroperoxide in benzene in the presence of a catalytic amount of Triton-B. Compounds (**2a-e**) were formed in moderate yields and were easily identified on the basis of their ir (1780 - 1790 cm^{-1}, C=O) and ^1H nmr spectra (δ 4.6 - 5.1, hydrogen on the epoxide ring).



1 a-e



2 a-e



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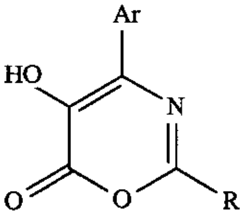


3 a-f

1, 2, 3	R	Ar
a	C_6H_5	C_6H_5
b	C_6H_5	$C_6H_4Cl(4)$
c	n-C_3H_7	$C_6H_4Cl(4)$
d	CH_3	$C_6H_4Cl(4)$
e	CH_3	$C_6H_4CH_3(4)$
f	C_6H_5	$C_6H_4CH_3(4)$

The starting olefins (**1**) were found to be the respective *Z*-form. However, since it is known[5] that the epoxidation reaction with *t*-butyl hydroperoxide is not stereospecific, two diastereoisomeric products were to be expected. This is indeed the case for **2d,e**, whereas **2a-c** were isolated after crystallization as the respective single diastereoisomers. Compounds (**2a-e**) were relatively stable solids which could be stored for long periods at low temperature in the absence of moisture. On heating **2a** in refluxing anhydrous toluene for some hours it underwent a transformation affording 2,4-diphenyl-5-hydroxy-1,3-oxazin-6(6*H*)-one (**3a**) as the main product in about 20% yield. A similar result was obtained in the presence of *p*-toluenesulfonic acid as an acidic catalyst, but a far better yield (54%) could be reached when the reaction was done in the same solvent in the presence of a lithium salt (anhydrous lithium perchlorate or acetate). By operating under these conditions products (**3b-e**) were also obtained from the corresponding epoxides. However, good yields could be obtained only starting from diaryl substituted epoxides. The structures of compounds (**3**) which, as far as we are aware, represent a new class of substituted 5-hydroxy-1,3-oxazin-6(6*H*)-ones, were inferred from analytical and spectroscopic data. The ir spectrum shows a band at 3350-3300 cm^{-1} associated with the OH group, a band at 1720-1690 cm^{-1} corresponding to the C=O group and an absorption at 1630-1610 cm^{-1} (C=N). From a X-ray single crystal diffraction study the structure of compound (**3a**) was unequivocally established (Figure 1).

Compound (**3a**) was crystallized from ethyl acetate yielding a mixture of two different crystalline forms which have been separated for the purposes of the crystallographic analysis manually under the microscope. Both forms have been examined by X-ray diffractometry.The *crystalline form A* has the space group $P2_1/C$ (N°14) with a = 5.676, b = 27.165, c = 8.489 Å; β = 107.84°; V = 1246 $Å^3$. Each cell contains four molecules. The *crystalline form B* has the space group P1 (N°2) with a = 8.9150, b = 9.949, c = 15.01 Å ; α = 78.43, β = 83.82, γ = 75.52°; V = 1261.0 Å^3. Each cell contains four molecules, i.e. two chemically identical but crystallographically distinct molecules. The indipendent molecules in the *crystalline form B* have a slightly different geometry.[6]

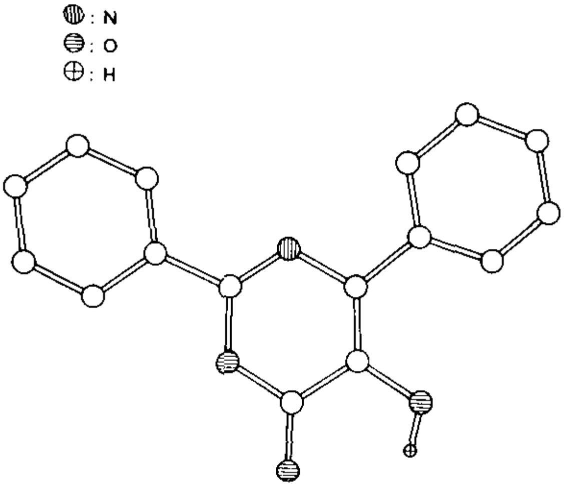


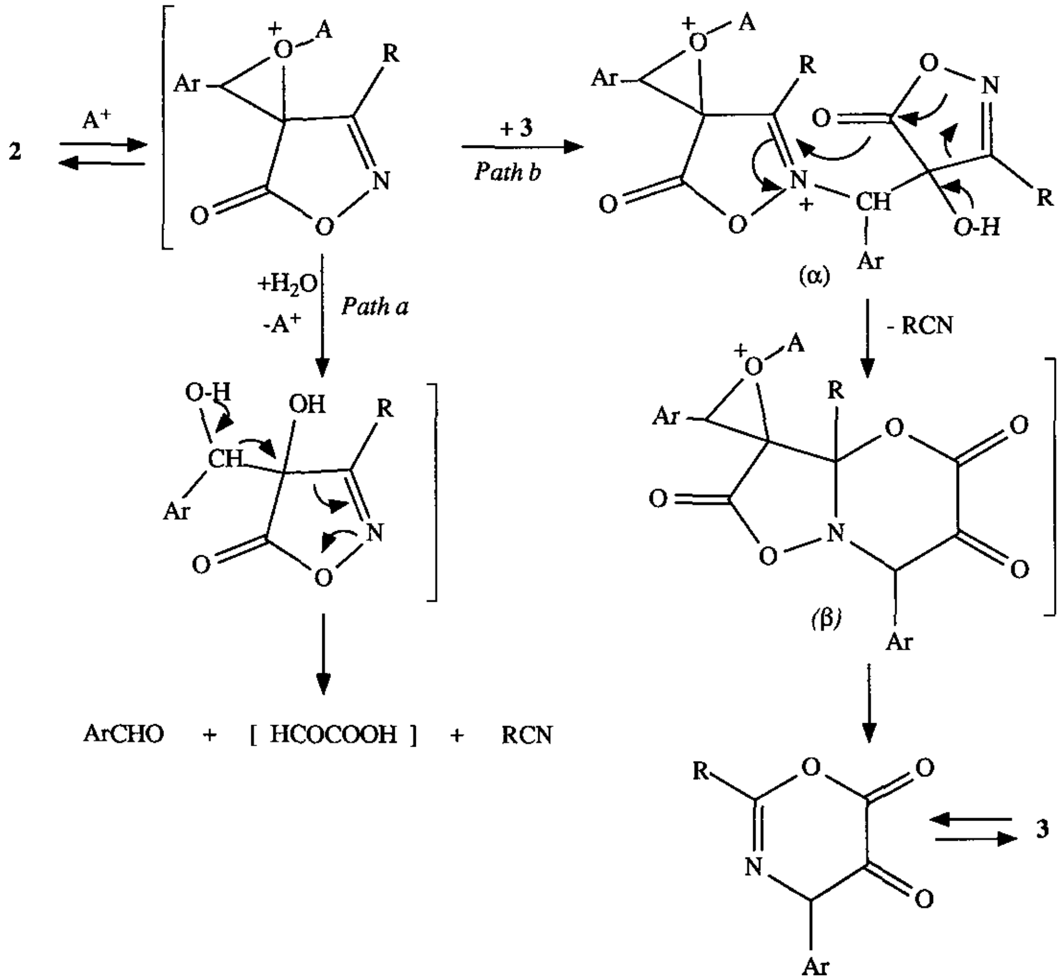
Figure (1). View of molecule (**3a**) as determined by X-ray analysis. Except for the OH group all H atoms have been omitted for the sake of clarity

Upon treatment with methyl iodide in acetone and sodium carbonate, compound (**3a**) was readily methylated to give **4**.

When **2a** and **2b** were treated with 70% perchloric acid in chloroform a complete degradation was observed. Benzaldehyde and 4-chlorobenzaldehyde (for **2a** and **2b**, respectively) and benzonitrile could be identified in the reaction mixture by gas chromatography. The formation of these decomposition products can be rationalized by *path a* indicated in the Scheme. As far as the reaction pathway which leads to compounds (**3**) is concerned it has to be taken into account that in the final products the atom sequence existing in the starting heterocycles is not mantained. Accordingly a profound rearrangement might occur. A rationalization of this reaction is depicted in the Scheme as *path b*. This reaction mechanism involves an intermolecular condensation in which the nucleophilic N-atom adds to the oxirane ring of another molecule. The intermediate (α) so formed undergoes opening of one isoxazolone ring accompanied by nitrile elimination and cyclization on the C=N bond producing the tricyclic intermediate (β) from which the final product is obtained through elimination of

CO_2 (identified by barium hydroxide test) and of the oxirane moiety followed by enolization. The intermolecular course of the reaction has been demonstrated by the reaction of an equimolecular mixture of compounds (**2b**) and (**2e**). After chromatographic separation of the reaction mixture two fractions could be isolated, the first containing oxazinones (**3d,e**), and the second containing (**3b,f**). All compounds were identified by their signals in the ^1H nmr spectrum. Clearly compounds (**3d**) and (**3f**) can be formed only by an intermolecular reaction. Recently we have reported another case of formation of 1,3-oxazin-6-one derivatives by rearrangement of the isoxazolone ring.[7] Compounds (**3**) were found essentially stable to perchloric acid under the conditions which lead to the degradation of oxiranes (**2**) according to *path a*, thus ruling out the intermediacy of oxazinone compounds in this process.

Scheme



EXPERIMENTAL SECTION

Melting points: Büchi 510 (capillary) apparatus. Ir spectra: PYE UNICAM SP3-200S Philips spectrophotometer. ^{1}H Nmr experiments are performed on Bruker AC200 and EM-390 Varian instruments. Column chromatography: silica gel with the eluent indicated. Isoxazolones (**1a**,[2] **1b**,[3] **1d,e**[4]) are knowns.

4-(4-Chlorobenzylidene)-3-propylisoxazol-5(*4H*)-one (1c) --- A solution of 3-propylisoxazol-5(*4H*)-one (6.0 g, 47.0 mmol), 4-chlorobenzaldehyde (6.6 g, 47.0 mmol) and a catalytic amount of piperidine in EtOH (50 ml) was refluxed for 30 min. After cooling the yellow solid was filtered and recrystallized from acetic acid yielding **1c** (1.3 g, 11%); mp 106-108 °C. Ir (nujol) ν_{max}: 1720 (C=O) cm^{-1}. ^{1}H Nmr ($CDCl_3$) δ: 1.0 (t, J = 6 Hz, 3H, CH_3), 1.4-2.7 (m, 2H, $\underline{CH_2}$-CH_3), 2.4-2.8 (m, 3H, $\underline{CH_2}$-C_2H_5 and CH),7.3-8.4 (m, 4H, H_{arom}). *Anal.* Calcd for $C_{13}H_{12}NO_2Cl$: C 62.52; H 4.84; N 5.61. Found: C 62.41; H 4.95; N 5.49.

6-Aza-1,5-dioxaspiro[2.4]hept-6-en-4-ones (2a-e); General Procedure: --- Compound (**1a-e**) (12.0 mmol) was suspended in benzene (50 ml). A solution of *t*-butyl hydroperoxide (12.0 mmol, 70%) and a catalytic amount of Triton-B in benzene (20 ml) was added dropwise to the suspension at room temperature in 10 min and stirring is continued for the time indicated. The organic layer was washed with water and then with 10% solution of sodium hydrogen sulfite, dried over Na_2SO_4 and evaporated under reduced pressure. Compounds (**2a,c-e**) were obtained after crystallization with the solvent indicated; pure compound (**2b**) crystallized directly from the reaction mixture. Yields, physical, spectral and analytical data are given in Table 1.

5-Hydroxy-1,3-oxazin-6(*6H*)-ones (3a-e); General Procedure: --- To a suspension of anhydrous $LiClO_4$ (1.5 mmol) in anhydrous boiling toluene (20 ml), under nitrogen, compound (**2a-e**) (15.0 mmol) was added and refluxed for 2-3 h. The reaction mixture was washed with water and the organic layer dried over Na_2SO_4. After solvent evaporation, the crude mixture was chromatographed with CH_2Cl_2 yielding a main fraction which, after crystallization with CH_2Cl_2/n-C_5H_{12}, affords pure **3a-e**. Yields, physical, spectral and analytical data are given in Table 1.

2,4-Diphenyl-5-methoxy-1,3-oxazin-6(*6H*)-one (4) --- To a solution of **3a** (300 mg, 1.1 mmol) in acetone (10 ml), CH_3I (0.07 ml, 1.1 mmol) and Na_2CO_3 (92 mg, 1.1 mmol) were added. The reaction mixture was stirred at room temperature for 1.5h. After solvent evaporation, the crude mixture was taken up with $CHCl_3$, washed

Table 1. 1,5-Dioxa-6-azaspiro[2.4]hept-6-en-4-ones (**2**).

Compd. No.	Reaction time (h)	Yield[a] (%)	mp (°C) Cryst. solvent	Molecular formula	Ir (nujol) ν (C=O) (cm^{-1})	^1H nmr ($CDCl_3$/TMS) δ(ppm)			Analysis Calcd (Found)		
						H_{arom}	CH	other	C	H	N
2a	4	75	153 (CH_2Cl_2/n-C_5H_{12})	$C_{16}H_{11}NO_3$	1780	8.0-7.5	4.8	-	72.44 (72.57)	4.18 (4.22)	5.28 (5.13)
2b	3	45	148 (C_6H_6)	$C_{16}H_{10}NO_3Cl$	1790	8.0-7.2	5.1	-	64.12 (64.37)	3.36 (3.18)	4.67 (4.78)
2c	3	36	112-113 (CH_2Cl_2/n-C_5H_{12})	$C_{13}H_{12}NO_3Cl$	1780	7.5-7.3	4.6	2.5-1.0 (n-C_3H_7)	58.76 (59.01)	4.55 (4.79)	5.27 (5.45)
2d[b]	6	25	86 (CH_2Cl_2/n-C_5H_{12})	$C_{11}H_8NO_3Cl$	1780	7.5-7.3	4.8, 4.7	2.1, 1.5 (CH_3)	55.59 (55.26)	3.39 (3.33)	5.89 (5.72)
2e[b]	5	6	99 (($(C_2H_5)_2O$)	$C_{12}H_{11}NO_3$	1790	7.5-7.1	4.7, 4.6	2.4 (CH_3-Ar), 2.1, 1.5 (CH_3-3)	66.35 (66.26)	5.10 (5.08)	6.45 (6.37)

[a]Not optimized. [b]Mixture of two diastereoisomers.

Table 2. 5-Hydroxy-1,3-oxazin-6-ones (**3**).

Compd. No.	Yield[a] (%)	mp (°C)	Molecular formula	Ir (nujol) (cm^{-1})			^1H nmr ($CDCl_3$/TMS) δ (ppm)	Analysis Calcd (Found)		
				ν_{OH}	$\nu_{C=O}$	$\nu_{C=N}$		C	H	N
3a	54	225	$C_{16}H_{11}NO_3$	3350	1700	1620	8.2-7.4 (m, H_{arom} and OH)	72.44 (72.16)	4.18 (4.12)	5.28 (5.17)
3b	64	227	$C_{16}H_{10}NO_3Cl$	3310	1690	1610	[b] 8.3-7.4 (m, 9H, H_{arom}), 6.5 (s, 1H, OH)	64.12 (64.44)	3.36 (3.18)	4.67 (4.78)
3c	10	150	$C_{13}H_{12}NO_3Cl$	3330	1720	1630	8.2-7.3 (m, 4H, H_{arom}), 6.1 (s, 1H, OH), 2.7-1.0 (m, 7H, n-C_3H_7)	58.76 (59.07)	4.55 (4.63)	5.27 (5.40)
3d	10	187-189	$C_{11}H_8NO_3Cl$	3300	1690	1610	8.2-7.4 (m, 4H, H_{arom}), 5.8 (s, 1H, OH), 2.4 (s, 3H, CH_3)	55.59 (55.39)	3.39 (3.13)	5.89 (6.03)
3e	12	205	$C_{12}H_{11}NO_3$	3300	1710	1630	8.0-7.2 (m, 4H, H_{arom}), 5.7 (s, 1H, OH), 2.4, 2.3 (two s, 6H, CH_3)	66.35 (66.08)	5.10 (5.09)	6.45 (6.34)

[a]Not optimized. [b]DMSO.

with water and dried over Na_2SO_4. After solvent evaporation and crystallization of the crude mixture from CH_2Cl_2/n-C_5H_{12}, pure **4** (138 mg, 45%) was obtained; mp 118 °C. Ir (nujol) ν_{max}: 1740 (C=O) cm^{-1}. ^1H Nmr ($CDCl_3$) δ: 3.9 (s, 3H, CH_3), 7.5-8.3 (m, 10H, H_{arom}). *Anal.* Calcd for $C_{17}H_{13}NO_3$: C 73.12; H 4.66; N 5.02. Found: C 73.37; H 4.84; N 5.11.

X-Ray Analysis: Unit-cell dimension and X-ray diffracted intensity data for both *crystalline form A* and *B* of compound (**3a**) were mesured at room temperature on an Enraf-Nonius CAD4 diffractometer equipped with graphite-monochromated Mokα radiation (λ = 0.71073 Å). The structures were solved by direct methods with program MULTAN[8] and refined by least-squares methods using the SDP-Plus program package.[9] *Crystalline form A* D = 1.414 g/cm^3. Least-square refinement was used for the parameters of position and thermal motion. Refinement was made on 226 parameters with 2052 independent structure factors with I>0. WR = 0.035 for all 2052 data used. R = 0.0351 for 1250 reflection with I>2σ. *Crystalline form B* 8892 reflections were mesured of which 4446 were independent. 4112 of the independent reflections were above background (I>0). The structure was solved by the refining of 450 parameters in 4112 observations. WR = 0.038.

ACKNOWLEDGMENT

We thank Prof. R. Destro for X-Ray analysis.

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Received, 26th March, 1991