Preparation and Mechanism of Solvolysis of *N*-Hydroxy-α-oxobenzeneethanimidoyl Chloride, a 2-(Hydroxyimino)-1-phenylethan-1-one Derivative: Molecular Structure of α-Oxo-oximes (= α-(Hydroxyimino) Ketones)

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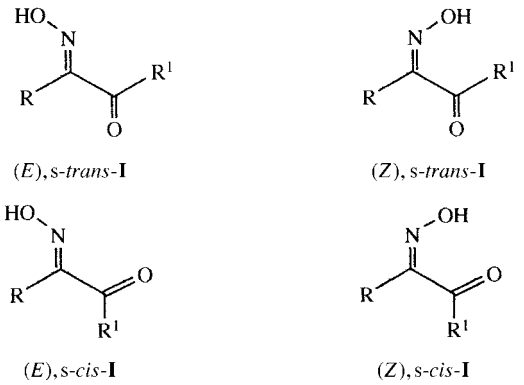
Acid-catalyzed methanolysis of *N*-hydroxy-α-oxobenzeneethanimidoyl chloride (**1**), a 2-(hydroxyimino)-1-phenylethan-1-one derivative obtained in one step from acetophenone, leads to a constant ratio of methyl α-oxobenzeneacetate (**2**) and methyl α-(hydroxyimino)benzeneacetate (**3**). $^{13}C(\alpha)$ Labelled [^{13}C]-**1** affords $^{13}C(\alpha)$ labelled [^{13}C]-**3**, thus discarding the hypothesis of its formation *via* 1,2-arene migration. The reported sequence opens a novel approach to phenylglyoxylic and mandelic acid esters (= α-oxobenzeneacetic and α-hydroxybenzeneacetic acid esters), from acetophenone. The molecular structures of **1** and **3** were determined by X-ray structure analysis and compared with previously reported crystallographic data of α-oxo-oximes (= α-(hydroxyimino) ketones) **4** and **6**–**8**. The unique stereoelectronic characteristics of the α-oxo-oxime moiety are discussed. All α-oxo-oximes share the following structural characteristics: (*E*)-configuration of the oxime C=N–OH bond (*i.e.* OH and C=O *trans*), the s-*trans* conformation of the oxo and imino moieties about the C(α)-C(=NOH) single bond, and *inter*molecular H-bonding. They differ from the isostructural β-diketone enols by the absence of resonance-assisted *intra*molecular H-bonding.

1. Introduction. – α-Oxo-oximes represent an important class of compounds due to their biological activity. They are also valuable prochiral precursors in the asymmetric hydrogenation to enantiomerically pure compounds; four principal stereoisomers and conformers are illustrated by the formulae **I**. Their preparation and the knowledge of the preferred configuration about the C=N bond of the oxime group and of the conformation of the oxo and imino moieties about the central C–C bond are, therefore, important for the understanding of biological and stereochemical aspects.

In the course of our search for combined catalytic and biocatalytic methods to produce enantiomerically pure α-substituted benzeneacetic acid derivatives, we discovered a one-step oxidative transformation of acetophenone to *N*-hydroxy-α-oxobenzeneethanimidoyl chloride (**1**), a 2-(hydroxyimino)-1-phenylethan-1-one derivative which has *trans*-orientation of the OH and C=O groups at the C=N bond (the configuration of the C=N bond of **1** is (*Z*)). Acid-catalyzed solvolysis of **1** afforded α-(hydroxyimino) ester **3**, with (*E*)-configuration of the C=N bond (OH and C=O in *trans*-position). We report on the preparation, elucidation of the mechanism of solvolysis, structure, and stereoelectronic properties of the title compounds.

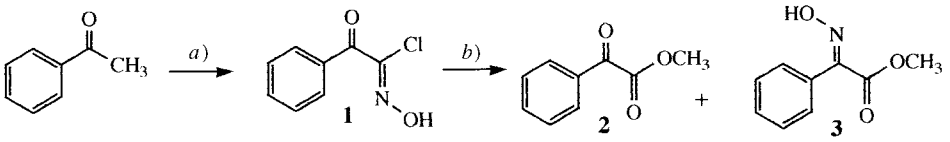


(*E*), s-*trans*-**I** (*Z*), s-*trans*-**I**

(*E*), s-*cis*-**I** (*Z*), s-*cis*-**I**

2. Results and Discussion. – 2.1. *Preparation and Solvolysis of* **1**. When a dispersion of acetophenone and a catalytic quantity of $NaNO_2$ in dilute hydrochloric acid was preheated to 65–70° and then nitric acid slowly added, a controllable exothermic reaction took place. Extraction of the product and crystallization afforded *N*-hydroxy-α-oxobenzeneethanimidoyl chloride (**1**) in *ca.* 50% yield (*Scheme 1*). Its structure was confirmed by ^{1}H- and ^{13}C-NMR and X-ray crystal-structure analysis.

Scheme 1



a) 15% aq. HCl/soln. HNO_3, $NaNO_2$, 70°. *b*) MeOH/conc. H_2SO_4 soln., 65°.

Direct oxidative chlorination can be explained by the oxidative capacity of the aqueous HCl/HNO_3 mixture (*aqua regis*) [1]. The effect of sodium nitrite is already known for the nitric-acid oxidation of acetophenone, and is rationalized as an initiation of formation of dinitrogen tetraoxide, a source of nitrosonium ion [2]. In such a strongly oxidizing system, the intermediary aldehyde oxime could be oxidized to the nitrile oxide $Ph-CO-C{=}N^+-O^-$, which undergoes attack by the Cl^- ion (addition of HCl). Interestingly, chlorination-oxidation to geminal chloro-nitro derivatives by *Oxone*® failed specifically with acetophenone oxime, affording decomposition products [3].

Acetophenone represents an easily available C_8 synthon of potential importance for the large-scale production of its higher oxidized congeners, in particular phenylglyoxylic acid (=α-oxobenzeneacetic acid), mandelic acid (=α-hydroxybenzeneacetic acid), and phenylglycine and its *N*-hydroxy derivatives. The simple, one-step chloronitrosation to **1** prompted us to examine the observed oxidative chlorination in the preparation of α-substituted benzeneacetic acid derivatives. On heating **1** in MeOH/conc. H_2SO_4 solution 1 : 1 at 65°, it was completely converted to the mixture **2**/**3**, which were easily separated by selective precipitation with an unpolar solvent; crude **3** was

isolated in *ca.* 15% yield when a concentrated CH_2Cl_2 extract of the reaction mixture was treated with hexane, and keto ester **2** was isolated in *ca.* 50% yield on evaporation of the filtrate and distillation *in vacuo*. Upon crystallization from $^{i}Pr_2O$, compound **3** exhibited ^{1}H- and ^{13}C-NMR spectra that could well be ascribed to the expected *N*-hydroxy-α-oxobenzeneethanimidic acid methyl ester; the elemental analysis corresponds to this isomeric structure. In the IR spectrum of **3**, however, the carbonyl stretching band is found at 1735 cm^{-1}, whereas in the starting chloride **1** it appears at 1660 cm^{-1}. Such a large shift cannot be explained by substitution of the Cl-atom by the MeO group; an X-ray single-crystal analysis was required to establish the structure of the oxime derivative **3** of methyl phenylglyoxylate (*Chapt. 2.4*).

Besides these two principal products, *ca.* 3% of methyl benzoate and *ca.* 4% of the dimethyl ketal of **2** were identified. Importantly, the ratio **2**/**3** of 3.3 : 1.0 did not change during the methanolysis of **1**, as confirmed by HPLC monitoring of the reaction. No *Beckmann* rearrangement product of **1** was found either, though a historically important analogue of **1**, with a Ph group in the place of the Cl-atom, allowed *Meisenheimer* to establish the *trans*-stereochemistry of this process [4][5]. It seems that this type of rearrangement is unfavoured in the case of **1** because of the electron-attracting effect of the Cl-atom.

It is important to note that all previously reported methods for the preparation of **3** require either specific conditions or inconvenient starting materials, comprising electrochemical reduction of methyl α-nitrobenzeneacetate [6], UV irradiation of β-bromo-β-nitrostyrene [7], or nitrosation of methyl benzeneacetate in aprotic solvent in the presence of a strong base [8]. In view of the well-documented methods for reduction of α-(hydroxyimino) esters to α-amino acids or α-(hydroxyamino) acids (see [9]), in particular by the complex reagent ($TiCl_3$/$NaBH_4$) [10], and in the light of the recently reported method for mild hydrolysis of oximes to ketones (MnO_2, hexane, room temperature) [11], this new two-step transformation of acetophenone, if it selectively yielded **2** or **3**, would offer a novel approach to α-O- and α-N-substituted benzeneacetic acid derivatives. We, therefore, undertook a detailed study of this process (see *Sect. 2.2.*).

2.2. *Mechanism of Solvolysis of* **1**. To obtain insight into the mechanism of formation of **2** and **3**, ^{13}C(α)-labeled **1** was prepared from (1-^{13}C)acetophenone and solvolysed under the same conditions as the non-labelled compound. We first assumed aryl participation in the formation of **3** (*Scheme 2*, *Pathway a*) and stabilization of a phenonium ion by delocalization of the positive charge. Methanolysis would result in 1,2-arene migration, a process well documented for 2-arylalkyl moieties with two sp^3 C-atoms in the chain [12], and consequently the ^{13}C-label of [^{13}C]-**1** should be found at *C*OOMe in **3**. However, all ^{13}C-label was found in *both* products **2** and **3** at C(α), thus eliminating the 1,2-arene migration pathway[1]). In the second experiment, ester **2** was reacted in MeOH/H_2SO_4 with an equimolar quantity of anhydrous hydroxylamine, under otherwise identical reaction conditions as in the solvolytic experiments;

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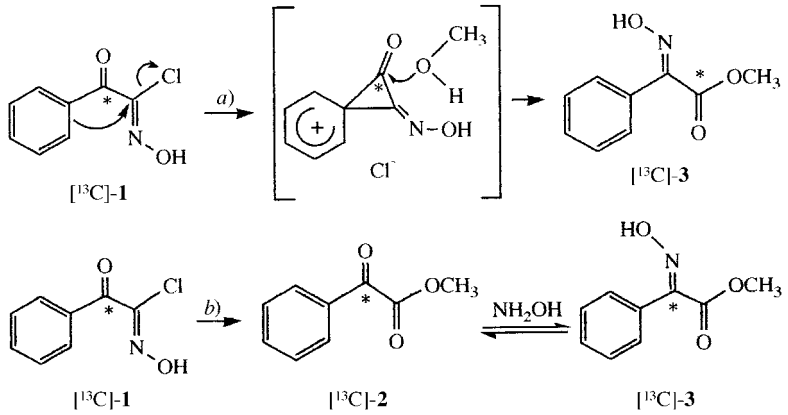
[1]) In the preliminary experiments, however, formation of carbocationic species from **1** and some congeners under cryogenic SbF_5 matrix conditions was observed by FT-IR, indicating that such species could exist under rearrangement conditions. Detailed spectroscopic and computational study of these species are in progress [15].

formation of **3** was observed at approximately the same rate as in the transformation of **1** into **3**. This result revealed an *inter*molecular pathway in the transformation of **1** to **3** (*Pathway b*), which is again surprising in view of the well known fact that oximes are generally prepared under weakly basic conditions [13], and that α-keto acids, on heating with hydroxylamine, decarboxylate to nitriles [14]. This finding discarded, however, the possibility to enhance the ratio **3**/**2** on solvolysis of **1**; on the contrary, dilution by water could assure exclusive formation of **2**.

Scheme 2



a) Aryl participation. *b*) *Inter*molecular pathway.

2.3. *Molecular and Crystal Structure of* **1** *and* **3**. The structures of **1** and **3** with the atom numbering are shown in *Figs. 1* and *2*. Characteristic bond lengths and angles are listed in *Table 1*. Planarity of the conjugated system in the molecules **1** and **3** (molecules *A* and *B*) is described in *Table 2*. H-Bonds with geometries are listed in *Table 3*, and their motifs are shown in *Figs. 3* and *4*.

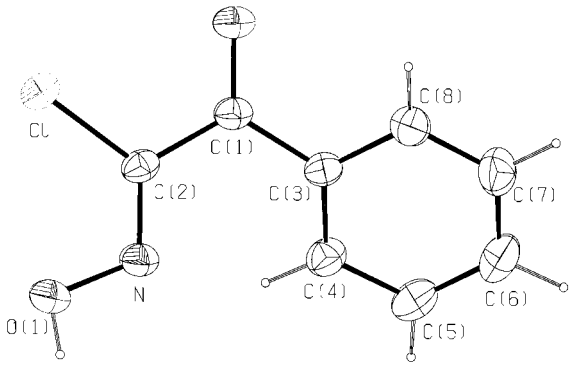


Fig. 1. *ORTEPII* [38] *view of* **1** *with the atom numbering* (arbitrary). The thermal ellipsoids are scaled at the 30% level.

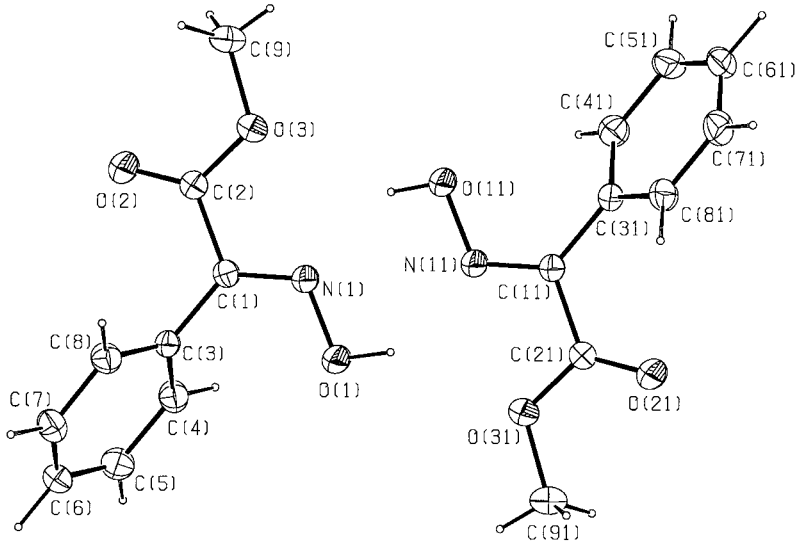


Fig. 2. *ORTEPII* [38] *view of* **3** (molecules *A* and *B*) *with the atom numbering* (arbitrary). The thermal ellipsoids are scaled at the 30% level. A pseudo inversion center, which relates some atoms of both conformers, is noticeable.

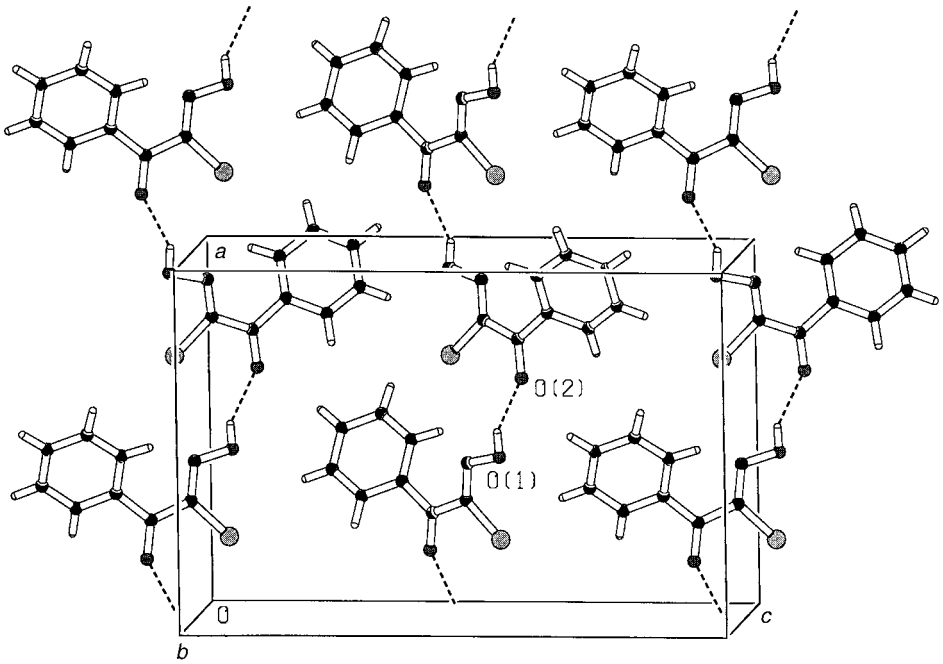


Fig. 3. *Crystal packing of* **1** *with infinite chain of molecules connected by hydrogen bonds* $O-H\cdots O$

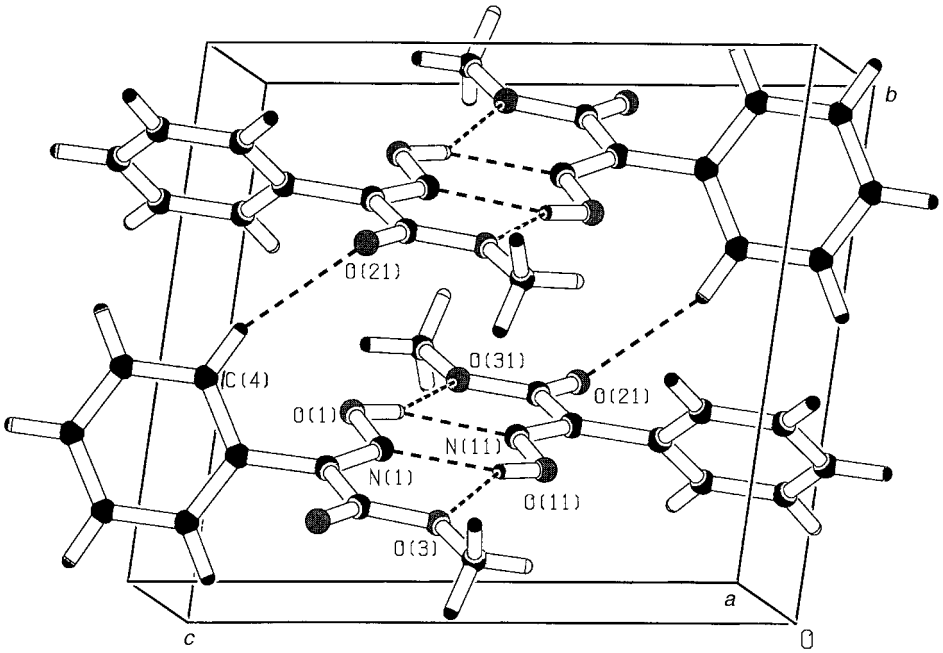


Fig. 4. *Crystal packing of* **4** *with hydrogen-bond network*

Table 1. *Selected Bond Lengths* [Å] *and Angles* [°] *of* **1** *and* **3**[2])

	1	**3**			
		Molecule *A*		Molecule *B*	
C(1)–C(3)	1.479(3)	C(1)–C(3)	1.485(1)	C(11)–C(31)	1.482(1)
N–C(2)	1.268(2)	N(1)–C(1)	1.280(2)	N(11)–C(11)	1.284(2)
N–O(1)	1.364(1)	N(1)–O(1)	1.384(2)	N(11)–O(11)	1.383(2)
O(1)–H(1)	0.80(2)	O(1)–H(1)	0.92(2)	O(11)–H(11)	0.88(2)
O(2)–C(1)	1.218(2)	O(2)–C(2)	1.193(2)	O(21)–C(21)	1.194(2)
Cl–C(2)	1.724(2)	O(3)–C(2)	1.335(2)	O(31)–C(21)	1.333(2)
		O(3)–C(9)	1.441(3)	O(31)–C(91)	1.443(3)
C(1)–C(2)	1.494(3)	C(1)–C(2)	1.500(2)	C(11)–C(21)	1.501(2)
C(arom.)–C(arom.)[a])	1.380(3)		1.384(2)		1.385(2)
C(2)–C(1)–C(3)	121.0(2)	C(2)–C(1)–C(3)	119.1(1)	C(21)–C(11)–C(31)	119.6(1)
C(3)–C(1)–O(2)	120.3(2)	C(3)–C(1)–N(1)	126.7(1)	C(31)–C(11)–N(11)	127.3(1)
O(1)–N–C(2)	113.3(1)	O(1)–N(1)–C(1)	114.7(1)	O(11)–N(11)–C(11)	115.0(1)
Cl–C(2)–C(1)	115.9(1)	O(3)–C(2)–C(1)	112.0(1)	O(31)–C(21)–C(11)	112.3(1)
O(2)–C(1)–C(2)	118.7(2)	N(1)–C(1)–C(2)	114.1(1)	N(11)–C(11)–C(21)	113.0(1)
N–C(2)–C(1)	120.3(2)	O(2)–C(2)–C(1)	123.4(1)	O(21)–C(21)–C(11)	124.0(1)
N–C(2)–Cl	123.8(1)	O(2)–C(2)–O(3)	124.5(1)	O(21)–C(21)–O(31)	123.7(1)
		C(2)–O(3)–C(9)	116.0(1)	C(21)–O(31)–C(91)	115.9(1)

[a]) Mean value.

[2]) Arbitrary numbering.

Table 2. *Planarity of the Conjugated Systems in* **1** *and* **3**: *Deviations of the Atoms from the Best Least-Squares Planes* [Å][a])[2])

1		**3**			
		Molecule *A*		Molecule *B*	
O(2)*	0.031(2)	O(2)*	0.038(2)	O(21)*	−0.016(1)
N*	0.031(2)	N(1)*	0.033(1)	N(11)*	−0.013(1)
C(1)*	−0.031(2)	C(1)*	−0.027(1)	C(11)*	0.010(1)
C(2)*	−0.032(2)	C(2)*	−0.044(1)	C(21)*	0.018(1)
O(1)	0.072(2)	O(1)	0.067(1)	O(11)	−0.088(1)
C(3)	−0.070(2)	C(3)	−0.075(1)	C(31)	0.034(1)
Cl	−0.0506(6)	O(3)	−0.152(1)	O(31)	0.069(1)

[a]) Atoms in the best least-squares planes are marked with an asterisk.

Table 3. *Hydrogen Bonds and C−H···O(N) Contacts for* **1** *and* **3**[2])

	D···*A* [Å]	*D*−H [Å]	H···*A* [Å]	*D*−H···A [°]	Symmetry operation on *A*
Compound **1**:					
O(1)−H(1)···O(2)	2.708(2)	0.80(2)	2.00(2)	150(2)	1/2+*x*, 1/2 − *y*, 1 − *z*
C(4)−H(4)···N	2.943(2)	0.94(2)	2.44(2)	113(2)	*x*, *y*, *z*
Compound **3**:					
(*A*) O(1)−H(1)···O(31) (*B*)	3.249(2)	0.92(2)	2.42(2)	150(2)	*x*, *y*, *z*
(*A*) O(1)−H(1)···N(11) (*B*)	2.806(2)	0.92(2)	2.02(2)	142(2)	*x*, *y*, *z*
(*B*) O(11)−H(11)···O(3) (*A*)	3.218(2)	0.88(2)	2.46(2)	145(2)	*x*, *y*, *z*
(*B*) O(11)−H(11)···N(1) (*A*)	2.774(2)	0.88(2)	2.00(2)	146(2)	*x*, *y*, *z*
(*A*) C(4)−H(4)···O(21) (*B*)	3.465(2)	0.96(2)	2.55(2)	159(1)	2 − *x*, 1 − *y*, 1 − *z*
(*B*) C(41)−H(41)···O(11) (*B*)	2.885(2)	0.96(2)	2.57(2)	99(1)	*x*, *y*, *z*
(*B*) C(81)−H(81)···O(21) (*B*)	2.990(2)	1.00(2)	2.64(2)	101(1)	*x*, *y*, *z*

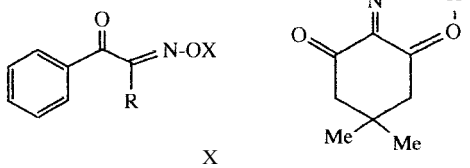
The molecular structure of **1** is characterized by the *trans*-orientation of the OH and C(2)=O[2]) moieties about the C=N bond, and by the s-*trans* conformation of the oxo and imino groups about the C(1)=C(2)[2]) bond, preventing an intramolecular H-bond (*Fig. 1*). Instead, a C−H···N intramolecular interaction involving an aromatic proton occurs (*Table 3*). The angle between least-squares plane of the conjugated system and the benzene ring is 38.3(1)°.

In the crystal structure of **3**, there are two conformers (molecules *A* and *B*). The torsion angles about the bond (Ph)C−C(sp[2]), *i.e.*, C(1)−C(3)[2]) in molecule *A* and C(11)−C(31)[2]) in molecule *B*, are −64.0(2) and −47.4(2)°, respectively. The relative orientations of the substituents in both molecules *A* and *B* (*Fig. 2*) about the N(1)=C(1) bond are *cis* for OH and Ph. About the bonds C(1)−C(2) and C(11)−C(21), the oxo and Ph groups are s-*cis*. The angles between best least-squares planes (as defined in *Table 2*) of the conjugated systems and benzene rings are 66.5(1) (molecule *A*) and 46.7(1)° (molecule *B*).

The crystal packing of **1** is simple, with an infinite chain of H-bonds (O−H···O) along the *a* axis (*Fig. 3*, *Table 3*). In the crystal packing of **3** (*Fig. 4*) three-centered (bifurcated) H-bonds (O−H···O and O−H···N) act between molecules *A* and *B* forming a dimer (*Table 3*) of $R_2^2(12)$ ring aggregate [16]. The interaction of (Ph)C−H ···O=C connects dimers into a discrete tetramer.

2.4. *Structure and Stereoelectronic Properties.* – α-Oxo-oximes can exhibit structural isomerism between the oxime and nitroso form, as well as configurational (E/Z) and conformational (s-*cis*/s-*trans*) isomerism. Intramolecular H-bonding has been postulated for some α-substituted derivatives of α-(hydroxyimino)acetophenone (= 2-(hydroxyimino)-1-phenylethan-1-one = α-isonitrosoacetophenone, **4**) [17], which is structurally similar to acetylcholin esterase (AChE) substrates. It has even been argued that the therapeutic activity of 4-bromobenzothiohydroxamic acids, which can be considered an α-(alkylthio)-α-(hydroxyimino) derivative of acetophenone, is based on intramolecular H-bonding [18]. This, in particular, applies to acetophenone derivative **5** with an α-(alkylthio) group and an ω-terminal tertiary-amine functionality, known as a strong inhibitor of AChE [18b].

The data bank of the *Cambridge Crystallographic Data Centre* reveals, however, that none of the five reported structures of nonsymmetric α-oxo-oximes, *i.e.* **4** and **6**–**9**, possess the (Z)-configuration ((E) for **1** and **9**) required for intramolecular H-bonding (*Table 4*) [19]. The non-symmetric oximes 2-(hydroxyimino)-1-phenylethan-1-one (**4**) [20], 4-bromobenzoate **6** of benzil monooxime [21], 1-phenylpropane-1,2-dione 2-oxime (**7**) [22], 1-phenylbutane-1,2,3-trione 2-oxime (**8**) [23], and phenyl *N*-hydroxy-α-oxobenzene ethanimidothioate (**9**) [24], are present in the (E)-configuration ((Z) for **1** and **9**), *i.e.*, *trans*-orientation of the OH and CO groups, and the s-*trans*-conformation in the solid state, and were previously regarded as less stable stereoisomers and conformers [25]. For the two symmetric α,α'-dioxo-oximes **10** and **11**, H-bonding to one oxo group should be obligatory; however, it is found to be weak.



	R	X
4	H	H
5	$CH_2CH_2N(CH_2CH_3)_2 \cdot HCl$	H
6	Ph	4-BrC_6H_4CO
7	Me	H
8	MeC	H
9	PhS	H

10

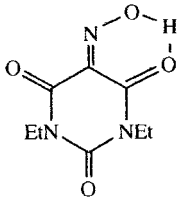


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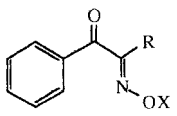
Table 4. *Solid-State Configuration and Conformation of α-Oxo-oximes*

	R	X	Configuration[a])	Conformation[b])	Ref.
1	Cl	H	(Z)	s-*trans*	this work
4	H	H	(E)	s-*trans*	[20]
6	Ph	4-BrC_6H_4CO	(E)	s-*trans*	[21]
7	Me	H	(E)	s-*trans*	[22]
8	MeCO	H	(E)	s-*trans*	[23]
9	PhS	H	(Z)	s-*trans*	[24]



[a]) The relative position of the C=O and NOX moieties is *trans* in all cases.
[b]) The relation of the oxo and imino moieties is meant.

It is interesting that α-oxo-oximes **1**, **3**, and **6**–**9** are stable in their oxime forms, though they do not possess an H-atom at the C-atom bearing the NON= group. In simple oximes, usually, the lack of such an H-atom shifts the equilibrium towards the nitroso form [26]. The stabilization of an oxime form in α-oxo-oximes could be explained by a weak resonance interaction of the π-electrons within the oxo-(aza)enol system. α-Oxo-oximes prefer the *trans*-orientation of the OH and C=O moieties, forcing the lone pair at the N-atom and the substituent R at C(2) also to have the *trans*-orientation. The O-atom of an oxime ($=N-O^{\delta-}-H^{\delta+}$) can be regarded as nucleophilic towards protons, wherein the N-atom exhibits an α-effect enhancing this affinity, *i.e.* diminishing the acidity of oximes as compared with enoles. Examples of such α-effects in nucleophiles are known, *e.g.*, for $HO-O^-$, $Me_2C=N-O^-$, and NH_2-NH_2 [27]; it could be explained either by the ground-state stabilization of the nucleophile by repulsion between the adjacent pairs of electrons [28] or by transition-state stabilization by an extra pair of electrons [29].

There is another interesting aspect of the relative stability of the solid-state conformers of α-oxo-oximes; dipole-dipole interaction favors s-*trans*-conformation around the single C–C bond, whereas extended conjugation and diminished σ-π repulsive interactions determine the (*E*)-configuration around the C=N bond. It is known that 1,2-dicarbonyl compounds in the diketo form prefer very much the s-*trans*-conformation [30], wherein two electronegative O-atoms are at the maximum possible distance and two carbonyl dipoles are opposed, and in that respect they resemble α-oxo-oximes. However, more a stable form of β-diketones mono-enols, α-oxo-oximes, are π-conjugated compounds that obey the resonance-assisted H-bonding (RAHB) model [31]. This model reflects synergistic reinforcement of H-bonding and π-delocalization. In β-diketone enols, two resonance forms are structurally and energetically nearly equivalent. When they are not equivalent, the H-bond strength is reduced and lengthening of the O–H···O H-bond occurs [32]. This situation is found in the O=C–C=N–OH unit of α-oxo-oximes [31c], and therefore, only in the symmetric compounds **10** and **11**, where the (hydroxyimino) group is available to one of two flanking α-oxo groups, weak *intra*molecular H-bonding is observed. In the oxime tautomer, more stable than the nitroso form [33], the O=C–C=N–OH unit appears weakly delocalized. Obviously, *intra*molecular H-bonding, present in all-C β-diketone enols, is perturbed by the heteroatom in α-oxo-oximes, which introduces molecular asymmetry.

Conclusions. – The reported sequence of reactions allows the simple preparation of phenylglyoxylic ester **2**, and thus an approach to racemic and optically active mandelic acid esters from acetophenone. Since the formation of (hydroxyimino) ester **3** represents a reversible pathway from **2** and hydroxylamine, the solvolytic process cannot be guided towards exclusive formation of **3**, an otherwise important intermediate for racemic and optically active phenylglycine and its *N*-hydroxy derivative. Collected structural data for α-oxo-oximes **1** and **3**, as well as all reported data for nonsymmetric α-oxo-oximes **4** and **6**–**9**, reveal their preference for the (*E*)-configuration about the C=N bond (*i.e.*, OH and C=O *trans*) and for the s-*trans*-conformation of the oxo and imino groups about the C(α)–C(=NOH) single bond, in contrast to the preferred molecular structure of their all-C analogues, the β-dicarbonyl

compounds. This finding questions the earlier assumed molecular topology of some *N*-hydroxy-α-oxocarboximidic acid derivatives [18], which was considered to be essential for their therapeutic effect. The molecular structure of α-oxo-oximes reflects the following stereoelectronic characteristics: *a*) repulsive σ-π interaction that stabilizes the (*E*)-configuration of the C=N bond, and repulsive dipole-dipole interaction between two double bonds which favors the s-*trans*-conformation of the oxo and amino groups, opposite to those adopted by their all-C analogues, the β-dicarbonyl compounds, *b*) the α-effect of the N-atom on the acidity, *i.e.* a reduced H-bonding capacity of the oxime OH group, and *c*) the absence of resonance-assisted H-bonding (RAHB).

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Experimental Part

General. HPLC: *HP-1050* chromatograph with *Nucleosil-100-C18* reversed-phase column; monitoring by *HP-1050-UV* detector, set up at 254 nm and connected to a *HP-3396A* integrator; t_R in min. GC: *HP-5890/II* instrument, with *HP-5* (20 m) capillary column; temp. gradient 70 → 250° at 15°/min. M.p.: *Electrothermal Apparatus*; not corrected. IR: *Perkin-Elmer-297* spectrometer for KBr pellets. ^{1}H- and ^{13}C-NMR: *Varian-Gemini-XL-300* spectrometer; δ in ppm rel. to $SiMe_4$, *J* in Hz.

N-*Hydroxy-α-oxobenzeneethanimidoyl Chloride* (**1**). To a stirred mixture of acetophenone (22.5 g, 0.16 mol) in a mixture of H_2O (40 ml) and conc. HCl soln. (30 ml), $NaNO_2$ (0.5 g, 0.006 mol) was added at r.t., followed by dropwise addition over 1 h of conc. HNO_3 soln. (12 ml, 0.17 mol) at 70°. Stirring was continued at 70° for additional 45 min. A sticky solid separated from the mixture which was collected by extraction with CH_2Cl_2 (3 × 100 ml). The combined extract was dried (Na_2SO_4) and concentrated to *ca*. 100 ml. Upon addition of hexane (*ca*. 150 ml), the precipitated product (97% by HPLC) was collected by filtration. On crystallization from CH_2Cl_2/hexane, pure **1** was obtained: 17.2 g (45%). M.p. 130–131° ([34]: m.p. 131–132°). IR: 3280, 1660, 1450, 1400, 1390, 1035, 855, 720. ^{1}H-NMR ((D$_6$)DMSO): 7.39–8.05 (*m*, 5 H); 13.67 (*s*, 1 H). ^{13}C-NMR ((D$_6$)DMSO): 128.6, 130.5, 133.6, 135.7, 136.7, 184.6.

Methyl α-Oxobenzeneacetate (**2**) *and Methyl α-(Hydroxyimino)benzeneacetate* (**3**). To **1** (10.0 g, 0.055 mol) in MeOH (60 ml), conc. H_2SO_4 soln. (60 ml) was added dropwise over 15 min. The mixture was stirred for another 5 h at 65° (HPLC monitoring: disappearance of **1** and formation of **2**/**3** *ca*. 3:1). On cooling to r.t., the mixture was poured onto ice-water (200 g). The resulting slurry was extracted with CH_2Cl_2 (3 × 50 ml), the extract dried and concentrated to *ca*. 40 ml, hexane (150 ml) slowly added and the precipitated **3** collected by filtration (98% by HPLC). The filtrate was washed with sat. aq. $NaHCO_3$ soln. and then with H_2O, dried, and evaporated. Pure **2** was obtained by distillation *in vacuo*.

Data of **2**. Yield 4.7 g (52%). B.p. 120–122°/10 Torr. IR (neat): 2960, 1740, 1690, 1595, 1450, 1205, 1000. ^{1}H-NMR ($CDCl_3$): 3.85 (*s*, 3 H); 7.18–7.91 (*m*, 5 H). ^{13}C-NMR ($CDCl_3$): 52.4, 128.7, 129.8, 132.2, 134.8, 163.9, 186.0.

Data of **3**. Yield 1.45 g (15%). M.p. 139–140° (crude); on crystallization from ^{i}Pr$_2$O, m.p. 142–143° ([35]: m.p. 145–148°). IR: 3220, 1740, 1435, 1200, 1020, 690. ^{1}H-NMR ((D$_6$)DMSO): 3.77 (*s*, 3 H); 7.42 (*s*, 5 H); 12.49 (br. *s*, 1 H). ^{13}C-NMR ((D$_6$)DMSO): 52.2, 128.1, 129.3, 130.2, 148.6, 164.5.

Monitoring of the Rearrangement of **1** *to* **2**/**3**. At 65°, **1** was stirred in conc. H_2SO_4 soln./MeOH 1:1 for 5 h. HPLC monitoring: *Nucleosil-C18* column, 50% aq. MeOH with 1% AcOH, flow rate of 0.8 ml/min; UV detection at 254 nm; t_R 14.1 (**1**), 9.4 (**2**) and 5.2 (**3**).

Monitoring of the Conversion of **2** *with Hydroxylamine to* **3**. Under the same conditions as for the methanolysis of **1**, **2** was treated with an equimolar quantity of hydroxylamine hydrochloride. HPLC monitoring: formation of **3** up to 10–15% of starting **1**. After 5 h, the reaction was stopped and **3** isolated in 7% yield and spectroscopically fully characterized.

1-Phenyl[1-^{13}C]ethan-1-one (= *[1-^{13}C]Acetophenone*. Starting from the labelled (1-^{13}C)acetic acid (0.5 ml; 99 atom-% ^{13}C; *Aldrich*) and AcOH (4.5 ml; total 5.25 g, 87.5 mmol) in dry benzene (5.0 ml), $SOCl_2$ (11.3 g, 96.5 mmol) was added dropwise at r.t. The mixture was stirred overnight and the reaction completed by addition of one drop of DMF and 2 h additional stirring. The resulting crude labelled acetyl chloride was added dropwise

Table 5. *Crystal Data and Details of the Structure Determination*

	1	**3**
Crystal data: Chemical formula	$C_8H_6NO_2Cl$	$C_9H_9NO_3$
M_r	183.59	179.18
a/Å	11.6120(7)	9.4681(5)
b/Å	7.937(2)	9.6809(6)
c/Å	17.717(2)	10.2338(3)
α/°		93.087(4)
β/°		94.942(3)
γ/°		110.490(4)
V/Å^3	1632.9(5)	871.86(8)
Z	8	4
D_c/g cm^{-3}	1.494	1.365
$F(000)$	752.0	376.0
Crystal system	orthorhombic	triclinic
Space group	*Pbca*	$P\bar{1}$
Crystal size/mm	0.12, 0.1, 0.1	0.1, 0.3, 0.3
μ (CuK_α)/cm^{-1}		8.7
μ (MoK_α)/cm^{-1}	4.2	
Data collection: Diffractometer	*Enraf-Nonius CAD4*	
Radiation/Å	Mo$K\alpha$($\lambda = 0.71069$)	Cu$K\alpha$($\lambda = 1.54184$)
Temperature/K	295(3)	
θ_{min}, θ_{max}/° for cell det.	5.55, 18.55	40, 45.5
No. of reflections used for cell det.	20	24
θ_{min}, θ_{max}/° for data coll.	2, 26	2, 74
$\omega/2\theta$ scan/°	$\Delta\omega = 0.31 + 0.84\tan\theta$	$\Delta\omega = 0.64 + 0.93\tan\theta$
hkl limits	−14, 0; −9, 0; −22, 0	−11, 11; −12, 0; −12, 12
No. measured refl.	1930	3749
No. total independent refl.	1651	3532
No. observed refl.	912	2856
Criterion for observed refl.	$\lvert F_o\rvert > 4\sigma(F_o)$	
Refinement: Refinement on F^2		
No. of parameters	133	307
$R(F)$, observed	0.032	0.052
$wR(F^2)$, all data[a])	0.089	0.161
Goodness of fit, S	0.893	1.096
Max. shift/error $(\Delta/\sigma)_{max}$	< 0.001	0.001, (z, H911)
Residual electron density, $\Delta\rho_{max}$, $\Delta\rho_{min}$ eÅ^{-3}	0.19, −0.26	0.25, −0.43

[a]) $w(\mathbf{1}) = 1/[\sigma^2(F_o^2 + (0.0438\cdot P)^2 + 0.0\cdot P]$, $P = (\max(F_o^2, 0) + 2F_c^2)/3$;
$w(\mathbf{3}) = 1/[\sigma^2(F_o^2 + (0.108\cdot P)^2 + 0.06\cdot P]$, $P = (\max(F_o^2, 0) + 2F_c^2)/3$.

at 10° to a slurry of $AlCl_3$ (16.0 g, 120 mmol) in dry benzene (5 ml). Upon 4 h stirring at r.t., the mixture was poured on ice/water, stirred until turbidity disappeared, and then extracted with hexane (2 × 25 ml). The combined extract was washed with H_2O, sat. $NaHCO_3$ soln., and then H_2O, dried, and evaporated. The crude product was distilled: 6.55 g (64.0%) of 1-phenyl[1-^{13}C]ethan-1-one. B.p. 80–83°/15 Torr. GLC: 98.5% pure. Quant. ^{13}C-NMR: 10% of ^{13}C-enrichment at C(1).

N-*Hydroxy-α-oxobenzene[α-^{13}C]ethanimidoyl Chloride* ([^{13}C]-(**1**). To the mixture of 1-phenyl[1-^{13}C]ethan-1-one (6.50 g, 54 mmol; 10% ^{13}C-enriched), conc. HCl soln. (12.0 ml), and H_2O (8.0 ml) at 70°, $NaNO_2$ (100 mg, 1.4 mmol) and 65% HNO_3 soln. (5.0 ml, 70°mmol) were added. After the exothermic reaction had ceased, the mixture was stirred at 70° for 1 h. Then the sticky residue was dissolved in $CHCl_3$ (70 ml), the soln. dried and concentrated to 20 ml, hexane (100 ml) slowly added, and the precipitated product collected by filtration, washed with hexane, and dried; 3.22 g (33%) of [^{13}C]-**1**. HPLC: 99% pure. Quant. ^{13}C-NMR: 10% ^{13}C-enrichment at C(α).

Methyl α-Oxobenzene[α-^{13}C]acetate ([^{13}C]-**2**) *and Methyl α-(Hydroxyimino)benzene[α-^{13}C]acetate* ([^{13}C]-**3**). Methanolysis and isolation of the products was performed as described for the non-labelled material. Quant. ^{13}C-NMR: 10% ^{13}C-enrichment at C(α) in both **2** and **3**. The position of the label was confirmed by ^{13}C,^{13}C coupling signals between C(α) and C(1) (benzene ring), and C(α) and *C*OOMe: J(C(α),C(1)) = 85 (**3**) and 74 (**2**), and J/C(α),*C*OOMe) = 56 (**3**) and 58 (**2**).

X-Ray Structure Determinations of **1** *and* **3**[3]. Compounds **1** and **3** were prepared for X-ray structure determination by crystallization: **1** was repeatedly crystallized from CH_2Cl_2/hexane *ca.* 1:1, **3** from $^{i}Pr_2O$. *Table 5* summarizes crystal data and experimental details of data collection and refinement. Intensities were measured on an *Enraf-Nonius-CAD-4* diffractometer with graphite-monochromated Cu$K\alpha$ radiation in the $\omega/2\theta$ scan mode. The intensity-controlled reflections were used each hour, whereas the crystal orientation was checked by two standard reflections each hundred reflections. There were no significant variations in intensity for standard reflections. The data were corrected for *Lorentz* and polarization effects with the program HELENA [36]. The structures were solved by SHELXH 86 [37] and refined on F^2 with SHELXH 97 [38]. The crystal-structure determination of **3** revealed two molecules *A* and *B* in the asymmetric unit. These two molecules are related by a pseudo inversion center; *ca.* 80% of the atoms follow the inversion symmetry operation. A free rotation about the bond (Ph)C–C results in two different conformers in the asymmetric unit. The H-atom coordinates were determined from the subsequent difference *Fourier* synthesis. Atomic scattering factors and anomalous dispersion values for the Cl-atom were those included in SHELXH 97 [38]. The molecular geometries were calculated by the program EUCLID [39]. Drawings were prepared by the program PLUTON incorporated in EUCLID and ORTEP [40].

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[3]) Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the *Cambridge Crystallographic Data Centre* as deposition Nos. CCDC-118768 and CCDC-118769. Copies of the data can be obtained, free of charge, on application to the *CCDC*, 12 Union Road, Cambridge CB2 1EZ UK (fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk).

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