The Effect of Solvent on Chemical-shift Non-equivalence of Diastereotopic Geminal Nuclei in (*pro*)^1-Chiral *N,N*-Disubstituted 5-Oxo-4-phenyl-2,5-dihydroisoxazol-2-ium-3-olates

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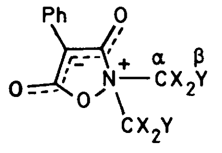
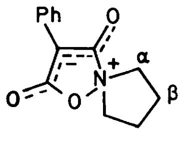
The ^{1}H and ^{13}C resonance shifts of the geminal nuclei in *N,N*-diethyl, -dibenzyl, -di-isopropyl, and -tetramethylene derivatives of 5-oxo-4-phenyl-2,5-dihydroisoxazol-2-ium-3-olates have been measured in various solvents and $(CD_3)_2SO$–$CDCl_3$ mixtures. It is concluded that the accidental isochrony of the geminal hydrogens of the *N,N*-diethyl derivative in $(CD_3)_2SO$ is not due to a change in conformation. The aim of this work is to discover whether the changes of the relevant chemical shifts are due to the change in the reaction field at the dipole of the molecule, which differs according to the change in dielectric constant of the medium. The use of solvents less polar than $(CD_3)_2SO$ as well as of some of higher polarity results in well separated anisochrony of the two geminal hydrogens. The different directions and magnitudes of the solvent effects on the chemical shifts of each of the nuclei in the compounds studied are attributed to their different angles, relative to the direction of the reaction field.



(1) X = H, Y = Me

(2) X = Me, Y = H

(3) X = H, Y = Ph



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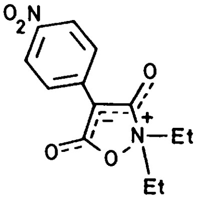

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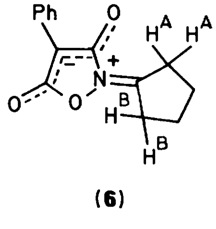

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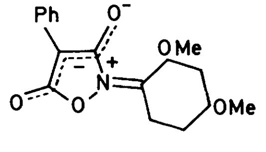

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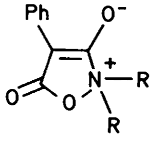


(8)

A (*pro*)^p-chiral object is defined by Mislow and Siegel[1] as any finite achiral object that can be desymmetrized into a chiral object by at most p ($p > 0$) stepwise replacements of a point by a differently labelled one; (*pro*)^n chirotopicity is defined in parallel for segments of the achiral object. In the molecules (**1**)—(**5**) both the carbons α to the nitrogen and the quaternary nitrogen itself are (*pro*)^1 chiral centres. Consequently, replacement of one of the two chemically identical groups on the α-carbon will bring about chirality at both centres. In other words, the two geminal hydrogens in (**1**), (**3**), and (**5**) as well as the two CH_3 groups in (**2**) are symmetrically non-equivalent regardless of whether or not there is free rotation around the N–C bond.

An important condition for an observable chemical shift between two such nuclei is the existence of either a magnetic- or an electric-field gradient.[2] Most of the works on geminal non-equivalence in the literature deal with compounds that have a chiral centre,[3–5] or sometimes restricted rotation.[6] The large selective-field gradient caused by the charged isoxazolium moiety has been shown recently[7] in ketisate, derived from 4-phenyldisic acid and cyclopentanone (**6**), where all four α-hydrogens of cyclopentanone were found to resonate at quite a low field with a difference $\delta_A - \delta_B$ of *ca.* 0.45 p.p.m. It seems that this effect is through space and could be a result of either the large dipole moment or a ring current associated with the resonating anion.

It will be shown that it is possible to explain the effect of solvent on this non-equivalence of the geminal nuclei in molecules (**1**)—(**5**) by the reaction-field theory.[8–10] It has already been stated by Laszlo,[11] when studying this theory, that the 'ideal molecule for such a study would have ... a large, permanent dipole moment and possess various types of nuclei differently oriented with regard to this vector and well separated and identifiable resonances.'

The idea of the reaction field explains the interaction between a polar solute and a polar or polarizable solvent.[8] Calculations,[8,12] give the reaction field at the centre of cavity as:

$$R = \rho(\varepsilon)\mu \qquad (1)$$

where μ is the molecular dipole moment and $\rho(\varepsilon)$ depends on the shape of the molecule and ε is the dielectric constant of the medium. It was also shown[13] that for an ellipsoidal molecule (a shape which will be approximately true for most organic molecules) the reaction field will be:

$$R = \frac{3}{abc}\xi_a[1 + (n^2 - 1)\xi_a]\frac{\varepsilon - 1}{\varepsilon - \beta}\cdot\mu \qquad (2)$$

where a, b, and c are the principal axes of the ellipsoid, and

$$\beta = \frac{n^2\xi_a}{1 - \xi_a}$$

ξ_a being a shape factor and n is the refractive index of the solute. On the other hand, it was agreed[10,11] also that, to a first approximation, the dependence of the magnetic shifting (Δ_X) of a nucleus X in a chemical bond (C–X) is linear with the projection of the electric field in the direction of the C–X bond:

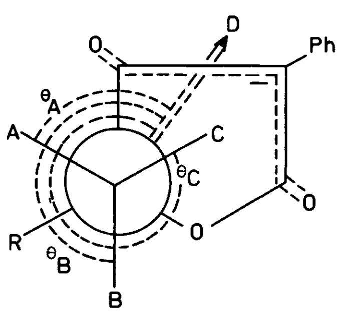


Figure 1. Newman projection of *N,N*-disubstituted 5-oxo-4-phenyl-2,5-dihydroisoxazol-2-ium-3-olates (**1**)—(**5**). A, B, and C are the three substituents on each α-carbon forming angles θ_A, θ_B, and θ_C respectively, with the dipole moment vector ***D***

$$\Delta_X \approx -K_E\, E \cos\theta \qquad (3)$$

where $E\cos\theta$ is the projection of an electric field E and K_E is a constant characteristic of the C–X covalent bond. The negative sign of K_E ensures that the magnetic shielding, in the case of a proton, is reduced if the direction of E is so as to reduce the electron density at the proton.

Results and Discussion

Molecule (**1**) which was described earlier[14] showed, to our surprise, isochrony of the two geminal protons in the n.m.r. spectrum taken in $(CD_3)_2SO$. However, non-equivalence of these nuclei was well illustrated in $CDCl_3$. A stepwise increase in the anisochrony on addition of $CDCl_3$ to $(CD_3)_2SO$ as well as by using less polar solvents (*e.g.* acetone and $[^2H_5]$THF) was observed. One explanation for this could be a change in conformation. However, this can probably be excluded by the absence of a significant temperature effect on the anisochrony in any of these solvents and solvent mixtures. The possibility that the two side chains on the quaternary nitrogen [in (**1**)—(**5**)] are not equivalent was excluded by the following observations. (*i*) The ^{13}C n.m.r. spectra of all these compounds, in all solvents and mixtures, showed that the C-α atoms were equivalent. The same was observed for C-β, except, of course, in (**2**), where the two carbons of each isopropyl group were not equivalent. (*ii*) The ^1H n.m.r. spectra of (**1**) and (**5**) in all solvents showed one triplet for all six protons for β-CH_3. In (**2**), the two protons of the CH groups were also found to be equivalent. Thus we were led to examine the validity of the reaction-field theory in this case and to check the generality of our conclusions by synthesizing compounds (**2**)—(**5**) and studying their n.m.r. spectra in solvents of varying dielectric constant, ε.

Examination of the ^1H n.m.r. spectra of (**1**) in different media indicated that the shifts of the various protons were affected by increasing the dielectric constant. This was also true for the two geminal protons. Owing to the influence of the reaction field on various nuclei in the same molecule, the ratio between the change in the chemical shift with the change in the solvent (Δ_{X_1}) of nuclei X_1, is essentially related [from equation (3)] to the cosines θ, for instance:

$$\frac{\Delta_{X_1}}{\Delta_{X_2}} = \frac{k_{E_1}\cos\theta_1}{k_{E_2}\cos\theta_2} \qquad (4)$$

where θ_1 and θ_2 are the projected angles between the vector ***R*** and C–X_1 and C–X_2 bonds, respectively.

Figure 1 depicts the Newman projection of molecules (**1**)—(**5**), in which the three substituents on the α-carbon are designated positions A, B, and C, respectively. It is assumed that the dipole moment is directed from the positive nitrogen to the resonating anion, closer to the oxygen at position 3. Using equations (3) and (4), it is possible to predict the location of each of the geminal nuclei and to estimate the relative projected angle between the C–H bond and the direction of the dipole moment and thus tell whether it occupies position A, B, or C. The assumption which was made about the direction of the dipole moment is based essentially on observations[7] in a similar dipole compound [(**7**)]. The C–O bond in position 3 was found by *X*-ray analysis to be longer than in position 5, suggesting that most of the negative charge is centred on this oxygen, *e.g.* that structure (**8**) is the major contribution to the charge distribution in the resonating anion.

From Tables 1 and 2 we can see that only in the case of compounds (**1**) and (**5**) does the anisochrony disappear in $(CD_3)_2SO$. In all other cases [(**2**)—(**4**)] it persists, but the magnitude is decreased. It is possible to explain the differences in behaviour of the various compounds by the different locations of the substituents around C-α (A, B, or C in Figure 1) and to derive this location by calculating the projected angles relative to the dipole moment of the molecule. It may be assumed that K_E [equation (3)] is identical for two geminal nuclei and that the averaged projected angles between the three substituents on C-α in (**1**) are 120° (see Figure 1). Therefore,

$$\frac{\Delta^s_A}{\Delta^s_B} = \frac{\cos(\theta_A + 180°)}{\cos(\theta_B + 180°)} \qquad (5)$$

and

$$\theta_B = \theta_A + 120° \qquad (6)$$

where Δ^s is the difference in the chemical shifts of the same protons in two solvents which differ in dielectric constant and where θ_A and θ_B are the projected angles between the C–H_A C–H_B bonds and the direction of the dipole moment, respectively. Using $\theta + 180°$ indicates that the bonds are in opposite directions to the vector ***R*** [see equation (4)].

By solving the two equations [(5) and (6)] for values of $\theta + 180°$ equation (7) is obtained. Because $\arctan\theta = \arctan(\theta + 180)$, the solution of equation (7) gives two values of which only one was found to be suitable. Direct solution for θ_B and θ_C could be obtained using equation (8) (see the Experimental section).

$$\theta_A = -\operatorname{Arctan}\left(\frac{2\Delta^s_B}{(\sqrt{3})\Delta^s_A} + \frac{1}{\sqrt{3}}\right). \qquad (7)$$

The calculated values for the angles, θ, relative to the dipole moment, are given in Table 2. The suggested predominant conformations of compounds (**1**)—(**5**) are shown in Figure 2. Some of the interesting conclusions about each of the studied compounds are the following:

Compounds (**1**) *and* (**5**). The calculated values of θ_A (93.8°) and θ_B (213.8°) in (**1**) suggest that the corresponding hydrogens assume positions A and B. Position C is therefore occupied by the CH_3 group and, as expected, achieves an *anti* conformation relative to the ethyl group. The large ratio $\cos\theta_B : \cos\theta_A$ explains the observed closing of the gap between the resonances of H_A and H_B. The *para*-nitro derivative (**5**) gave very similar results. It is supposed that the latter compound has a higher dipole moment. This explains the downfield shift of the resonances, but does not alter considerably the features concerning the non-equivalence and the solvent effect.

Compound (**2**). This new compound was synthesized and studied in order to find whether or not the anisochrony of the geminal methyl groups in the isopropyl substituents exists both in ^1H and ^{13}C magnetic resonances. The fact that this is indeed the case supplies further evidence for the assumption that this is a prochirality phenomenon. From the quantitative results it

Table 1. Chemical-shifts assignments and relative positions of groups in compounds (1)—(5) in $CDCl_3$ and $(CD_3)_2SO$

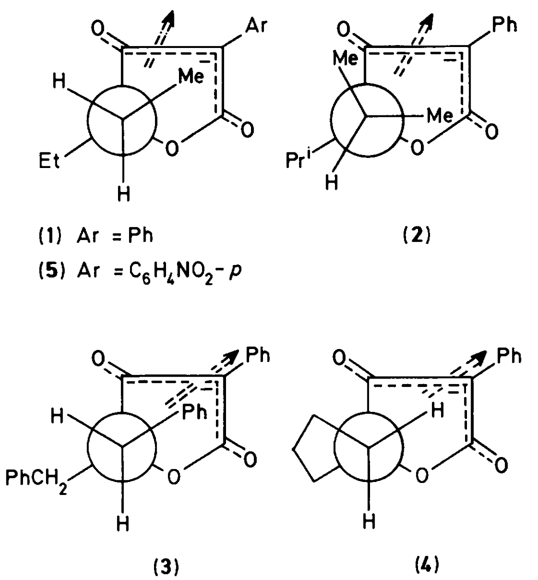
Solvent	Structure position	Group, δ/p.p.m. (1)	(2)	(3)	(4)	(5)
$CDCl_3$	A	H, 3.77 (8)	CH_3, 1.42 (2)	H, 4.81 (2)	CH_2, 2.31 (16)	H, 3.81 (8)
	B	H, 3.54 (8)	H, 4.14 (7)	H, 4.52 (2)	H, 3.64 (16)	H, 3.63 (8)
	C	CH_3, 1.33 (3)	CH_3, 1.46 (2)	Ph, 7.45—7.37	H, 4.08 (12)	CH_3, 1.36 (3)
	o	2 H, 8.03 (6)	2 H, 8.02 (6)	2 H, 7.62 (6)	2 H, 8.03 (6)	2 H, 8.25 (2)
	m	2 H, 7.35 (8)	2 H, 7.35 (8)	2 H, 7.21 (8)	2 H, 7.35 (8)	2 H, 9.21 (2)
	p	H, 7.14 (9)	H, 7.13 (9)	H, 7.05 (9)	H, 7.17 (9)	
$(CD_3)_2SO$	A	2 H, 3.79 (4)	CH_3, 1.32 (2)	H, 5.14 (2)	CH_2, 2.26 (16)	2 H, 3.84 (4)
	B		H, 4.30 (7)	H, 4.95 (2)	H, 3.85 (16)	
	C	CH_3, 1.15 (9)	CH_3, 1.35 (2)	Ph, 7.48—7.35	H, 3.98 (12)	CH_3, 1.17 (3)
	o	2 H, 7.92 (6)	2 H, 7.92 (6)	2 H, 7.48	2 H, 7.9 (6)	2 H, 8.22 (9)
	m	2 H, 7.32 (8)	2 H, 7.32 (8)	2 H, 7.15 (8)	2 H, 7.35 (8)	2 H, 8.18 (2)
	p	H, 7.11 (9)	2 H, 7.11 (9)	H, 6.95 (9)	H, 7.11 (9)	—

[a] Positions A, B, or C as described in Figure 2. [b] The number in parentheses is that of the signals observed. In an AB system, 2 is the number of signals for each H.

Table 2. Geminal anisochronies (Δ^n), solvent effects (Δ^s),[a] and calculated θ values[b]

Structure	$\Delta^n_{CDCl_3}$	Δ^n_{DMSO}	Δ^s_A	Δ^s_B	Δ^s_C	θ_A°	θ_B°	θ_C°	Δ^n_{THF}	$\Delta^n_{Acetone}$
					p.p.m.					
(1)	0.23	0	+0.02	+0.25	−0.18	93.8	213.8	(333.8)[c]	0.17	0.07
(2)	0.04	0.03	−0.10	+0.16	−0.11	61.6	(241.6)[c]	301.6	0.05	0.03
(3)	0.29	0.19	+0.33	+0.43	—	115.7	235.7	(355.7)[c]	0.27	0.22
(4)	0.45	0.13	−0.11	+0.21	−0.10	118.4	238.4	358.4		
(5)	0.18	0	+0.03	+0.21	−0.19	96.6	216.6	(336.6)[c]		

[a] Δ^s is the difference in p.p.m. $\delta[(CD_3)_2SO] - \delta(CDCl_3)$. [b] θ is the calculated angle between the group on C-α and the dipole vector ***D*** (Figure 1) using equations (5) and (6). [c] Calculated by subtracting 120° from the adjacent θ.



(1) Ar = Ph
(5) Ar = $C_6H_4NO_2$-*p*

(2)

(3)

(4)

Figure 2. Conformations of compounds (1)—(5) as derived by estimation of the angles between the substituents and the dipole moment of the molecules, using equation (7)

was possible to locate the two methyl groups at positions A and C. The ratio between the two Δ^s values, which was close to unity, suggested equal angles between the dipole moment and each of the methyl groups. In this conformation the lone hydrogen assumes position B, thus giving a large positive Δ^s value.

The most significant result is that, as expected for the more bulky isopropyl group, a certain deviation from the staggered conformation is observed. The calculated angles are distorted by *ca.* 32° as compared with those obtained for compound (**1**), allowing the methyl group at position A to avoid somewhat the bulky group.

Compound (**3**). Both geminal protons have positive Δ^s values of ratio *ca.* 4:3. The geminal non-equivalence is observable over a wide range of polarities; 0.29 p.p.m. for $CDCl_3$, 0.19 for $(CD_3)_2SO$. This is the consequence of the ratio $\Delta^s_A:\Delta^s_B$ and its positive sign.

Compound (**4**). This new compound was synthesized and studied here since, unlike the other four compounds, in this case the alkyl groups (*e.g.* the trimethylene bridge) cannot acquire an *anti* conformation and one of the geminal C–H bonds is thus forced into the direction of the anionic ring, *i.e.* position C (Figure 2). It is expected therefore to have a positive value for cos θ, as a result a negative Δ^s. Indeed, it is the only nucleus of which resonance is shifted upfield by increasing the dielectric constant of the medium. The large decrease in the geminal non-equivalence (0.32 p.p.m.) on going from $CDCl_3$ to $(CD_3)_2SO$ is the consequence of the negative sign and large value of Δ^s_B/Δ^s_C (2.1). The negative sign of Δ^s_A of the hydrogens on the β-CH_2 group and, interestingly, also its value are both in agreement with the θ_A calculated from θ_B and θ_C. In compounds (**1**)—(**3**) and (**5**) this kind of agreement is only qualitative, probably owing to the differences in the geometries of the C–H bonds in CH, CH_2, and CH_3 groups respectively, where also K_E might be different [equation (3)].

From the results obtained above it may be concluded that the change in the geminal anisochrony in each of these compounds with the change of solvent can be explained by the change in the reaction field with the change of the dielectric constant of the medium. The geminal groups in a certain molecule are influenced differently by the change in solvent because of the different directions of their bonds, relative to the direction of the reaction field (or the dipole moment). This was best shown in compound (**4**) where the rotation around the C–N bond is restricted.

The isochrony observed for compounds (**1**) and (**5**) in $(CD_3)_2SO$ is accidental. Assuming that compound (**5**) has a larger dipole moment enabled us to conclude also that it is not the value of the dipole moment that brings about a different solvent effect, but rather the relative angles, θ, between each of the geminal groups and the dipole moment vector. We may also add that the multiplicity of the signals of the aromatic protons in all these compounds (see Table 1) is probably the result not only of the anisogamy, but also the different directions of the protons relative to the dipole.

Experimental

N.m.r. measurements were taken with a 300 MHz Bruker spectrometer, model ASPECT 2000 relative to external $SiMe_4$. The chemical shifts of the AB systems were calculated by known methods.[15] Where complex systems [*e.g.* in (**1**) and (**4**)] were studied, the AB system was restored by spin–spin decoupling procedures. The concentrations of the samples in the deuterated solvents and mixtures were *ca.* 0.06 mol l^{-1}. The angles of the projected bonds relative to the direction of the dipole moment, *D*, were calculated by using the observed geminal Δ^s values and equation (7). When θ_A is first obtained, θ_B is derived by using equation (6). If the ratio Δ^s_B/Δ^s_A instead of Δ^s_A/Δ^s_B is used in equation (5), equation (7) should acquire a positive sign *e.g.*

$$\theta_B = \arctan\left(\frac{2\Delta^s_A}{(\sqrt{3})\Delta^s_B} + \frac{1}{\sqrt{3}}\right). \qquad (8)$$

depending on whether the measurements are taken clockwise or anticlockwise.

2,2-*Diethyl*-5-*oxo*-4-*phenyl*-2,5-*dihydroisoxazol*-2-*ium*-3-*olate* (**1**).—This product was prepared from 4-phenyldisic acid by alkylation with triethyloxonium fluoroborate in aqueous sodium hydrogen carbonate as described earlier.[14] A new route to the product by heating of the phenyldisic acid semihydrate[16] (3.7 g) in boiling saturated aqueous sodium hydrogen carbonate solution (200 ml) with an excess of diethyl sulphate for 2 h yielded the product (1 g) when the mixture was cooled. The product was recrystallized twice from $CHCl_3$–light petroleum (25% yield), m.p. 121 (lit.,[14] m.p. 121 °C), $\delta_C[(CD_3)_2SO]$ 168.24, 165.30, 130.50, 128.27, 124.84, 123.81, 73.68 (C^-), 55.76 (C-8), and 7.20 (CH_3); $\delta_C(CDCl_3)$ 168.53, 165.53, 130.06, 128.08, 125.26, 124.43, 77.41 (C^-), 56.22 (C-α), and 7.49 (CH_3).

2,2-*Di-isopropyl*-5-*oxo*-4-*phenyl*-2,5-*dihydroisoxazol*-2-*ium*-3-*olate* (**2**).—Chlorocarbonyl(phenyl)ketene[17] (0.36 g) was dissolved in dry dioxane (5 ml). A solution of di-isopropylhydroxylamine[18] (0.234 g) and triethylamine (0.404 g) in dry dioxane (5 ml) was added dropwise over 1 h with cooling at *ca.* the freezing point of dioxane. The mixture was stirred for an additional hour at room temperature and then concentrated under reduced pressure to a small volume. Saturated aqueous $NaHCO_3$ (20 ml) was added and the mixture was extracted with 3 portions of ether. The ethereal extract was dried (Na_2SO_4) and evaporated to a volume of 5 ml to which di-isopropyl ether (10 ml) was added. The solution was filtered free of precipitated impurities, concentrated under reduced pressure, and the product was purified by successive silica-gel chromatography, eluting with ethyl acetate. The pure product was obtained as an oil which crystallized out overnight at room temperature (0.26 g, 50%), m.p. 75 °C. It can be recrystallized from di-isopropyl ether without change in m.p.; $\nu_{max.}$(Nujol) 1 785, 1 700, and 1 600 cm^{-1}; $\delta_C[(CD_3)_2SO]$ 168.90, 166.15, 130.49, 128.00, 124.71, 123.68, 74.91 (C^-), 61.57 (C-α), 16.10 (CH_3), and 15.61 (CH_3); $\delta_C(CDCl_3)$ 169.45, 166.41, 130.17, 127.99, 124.99, 124.26, 75.70 (C^-), 61.64 (C-α), 16.52 (CH_3), and 15.93 (CH_3) (Found: C, 68.9; H, 7.25; N, 5.15. Calc. for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.35%).

2,2-*Dibenzyl*-5-*oxo*-4-*phenyl*-2,5-*dihydroisoxazol*-2-*ium*-3-*olate* (**3**).—4-Phenyldisic acid[16] semihydrate (1.76 g) was dissolved in water (130 ml) containing $NaHCO_3$ (7 g). Benzyl chloride (5.5 g) was added, the mixture was stirred and gently refluxed for 1 h. The sticky oil which resulted was separated by decantation, washed with water, and crystallized from ethanol and then from methanol (1.1 g, 30%), m.p. 185 °C; $\nu_{max.}$(Nujol) 1 790, 1 700, and 1 600 cm^{-1}; $\delta[(CD_3)_2SO]$ 167.45, 165.23, 132.18, 130.26, 130.09, 128.41, 127.84, 127.22, 124.68, 123.62, 75.05 (C^-), and 63.41 (C-α); $\delta_C(CDCl_3)$ 167.81, 166.27, 132.09, 130.67, 129.72, 128.88, 127.93, 125.99, 125.20, 124.64, 75.22 (C^-), and 64.00 (C-α) (Found: C, 77.35; H, 5.25; N, 4.05. Calc. for $C_{23}H_{19}NO_3$: C, 77.29; H, 5.36; N, 3.92%).

The same product could be prepared by the addition of chlorocarbonyl(phenyl)ketene[17] (0.36 g) to a solution of dibenzylhydroxylamine (0.2 g) in dioxane (5 ml) at 8—10 °C. The mixture was stirred overnight after which time the solvent was evaporated under reduced pressure. The residue was washed with aqueous sodium hydrogen carbonate and triturated with ethanol. The crystals formed were collected and recrystallized from methanol (0.1 g, 28%).

2,2-*Tetramethylene*-5-*oxo*-4-*phenyl*-2,5-*dihydroisoxazol*-2-*ium*-3-*olate* (**4**).—Chlorocarbonyl(phenyl)ketene[17] (0.9 g) was added, with cooling in ice, to a solution of *N*-hydroxypyrrolidine[19] (0.5 g) in dry THF (20 ml). The mixture was stirred for 30 min whereupon triethylamine (0.5 g) was added and the mixture was stirred for an additional hour. The solvent was evaporated under reduced pressure and the residue was dissolved in CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4), evaporated to dryness under reduced pressure, and the residue was crystallized from methanol (0.23 g, 20%), m.p. 163 °C; $\nu_{max.}$(Nujol) 1 780, 1 680, and 1 590 cm^{-1} (Found: C, 67.6; H, 5.6; N, 5.7. Calc. for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06%).

2,2-*Diethyl*-4-(4-*nitrophenyl*)-5-*oxo*-2,5-*dihydroisoxazol*-2-*ium*-3-*olate* (**5**).—4-(4-Nitrophenyl)disic acid[16] semihydrate (0.23 g) was boiled with stirring in water (200 ml) containing $NaHCO_3$ (10 g) and diethyl sulphate (20 ml) for 3 h. The precipitate which separated when the reaction was cooled was collected and recrystallized from CH_2Cl_2–cyclohexane (0.08 g, 28%), m.p. 192 °C; $\nu_{max.}$(Nujol) 1 780, 1 705, and 1 580 cm^{-1} (Found: C, 55.8; H, 4.85; N, 9.75. Calc. for $C_{13}H_{14}N_2O_5$: C, 56.11; H, 5.07; N, 10.07%).

References

1 K. Mislow and J. Siegel, *J. Am. Chem. Soc.*, 1984, **106**, 3319.
2 T. H. Siddall, *J. Phys. Chem.*, 1966, **70**, 2249.
3 For reviews see: E. L. Eliel, *Top. Curr. Chem.*, 1982, **105**, 1; W. B. Jennings, *Chem. Rev.*, 1975, **75**, 307.
4 J. Reisse, R. Ottinger, P. Bickart, and K. Mislow, *J. Am. Chem. Soc.*, 1978, **100**, 911.
5 G. M. Whitesides, J. J. Grocki, D. Holz, H. Steinberg, and J. D. Roberts, *J. Am. Chem. Soc.*, 1965, **87**, 1058.
6 J. Siegel, A. Gutierrez, W. B. Schweizer, O. Ermer, and K. Mislow, *J. Am. Chem. Soc.*, 1986, **108**, 1569.
7 G. Zvilichovsky and M. David, *Heterocycles*, 1987, **6**, 961.
8 L. Onsager, *J. Am. Chem. Soc.*, 1936, **58**, 1486; A. D. Buckingham, *Can. J. Chem.*, 1960, **38**, 300.
9 W. G. Schneider, *J. Phys. Chem.*, 1962, **66**, 2653.
10 J. I. Musher, *J. Chem. Phys.*, 1962, **37**, 34; P. Laszlo and J. I. Musher, *ibid.*, 1964, **41**, 3906.

11 P. Laszlo, *Prog. Nucl. Magn. Reson. Spectrosc.*, 1967, **3**, 231.
12 A. J. Dekker, *Physica*, 1946, **12**, 209; T. G. Scholte, *ibid.*, 1949, **15**, 437.
13 P. Diehl and R. Freeman, *Mol. Phys.*, 1961, **4**, 39.
14 G. Zvilichovsky, *J. Heterocycl. Chem.*, 1987, **24**, 465.
15 D. W. Mathieson, 'Nuclear Magnetic Resonance for Organic Chemists,' Academic Press, London, pp. 69—70.
16 G. Zvilichovsky, *Tetrahedron*, 1975, **31**, 1861.
17 S. Nakanishi and K. Butler, *Org. Prep. Proc. Int.*, 1975, 155.
18 G. Zinner and W. Kliegel, *Arch. Pharm.*, 1966, **299**, 166.
19 E. R. Blout, S. G. Cohen, and M. Green, *U.S.P.* 2,843,481 (*Chem. Abstr.*, 1958, **52**, 180441).

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