On the Reaction of Phenyldisic Acids with α,β-Unsaturated Carbonyl Compounds. Reversible Non-catalyzed Michael Addition and Ring Closure to Derivatives of 2*H*,7*H*-Isoxazolo[3,2-*b*][1,3]oxazine

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4-Aryl-3,5-dihyroxyisoxazoles which are strong organic acids add spontaneously to mesityl oxide to form 4-aryl-2-(1,1-dimethyl-3-oxobutyl)isoxazolidine-3,5-dione. This reaction was found to be reversible and the equilibrium is solvent dependent. These acids add to 2 moles of methyl vinyl ketone. The adducts obtained from mesityl oxide undergo ketalization to form derivatives of 2*H*,7*H*-isoxazolo[3,2-*b*][1,3]oxazine on exposure to alcohols. The rate of this ring closure reaction is dependent on the nature of the alcohol and on the nature of the substituent on the phenyl group which is at position 4 of the isoxazole ring. The mechanisms of the non catalyzed Michael addition and of the ketalization reaction are discussed. The structure of the polymers which are obtained by the reaction of phenyldisic acids with acrolein and crotonaldehyde is also discussed.

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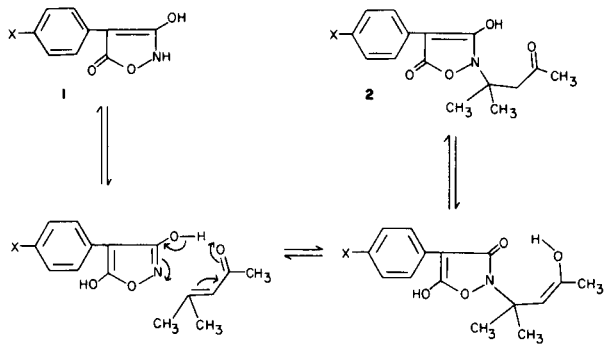
The isoxazole system in 4-aryl-3,5-dihydroxyisoxazoles (disic acids) (1) is very electron deficient. This fact as well as the neighboring group effect which was observed in this system (2), are responsible for the exceptional acidity and reactivity of these compounds (1,2). The electron deficiency of the dihydroxyisoxazole system is also reflected in the deshielding effect on the aromatic protons (1). These acids react spontaneously with aromatic aldehydes to yield the *N*-arylmethylideneisoxazolonium enolates which are refered also as aldisates (1,3). Cinnamaldehyde and citral gave aldisates. The reaction of unsubstituted phenyldisic acid with mesityl oxide was described earlier (2). The Michael addition product which results is subsequently cyclized in alcohol to a bicyclic ketal. The nature of these reactions were studied in the present work.

The addition reaction of phenyldisic acid and of its *p*-substituted derivatives to mesityl oxide was followed by the change of pmr signals. The vinylic proton of the mesityl oxide (δ = 6.0) is replaced by a methylenic signal. The two signals of the geminal methyl groups collapse into a singlet at a higher field. The combined signal of the exchangeable protons and of the moisture moves upfield as the reaction proceeds. The percent of conversion of phenyldisic acid (**1**, X = H) does not exceed 30% in dimethylsulfoxide at 35°. On the other hand when the pure addition product (**2**, X = H) is dissolved in DMSO a decomposition is observed. In the same conditions (*e.g.*, at 35°) the retro addition proceeds until the same equilibrium is reached. The decomposition occurs in other solvents as well, but the equilibrium constant is different. Thus in THF the addition proceeds almost to completion. The best yields are obtained when the reaction is carried out in mesityl oxide as the solvent.

Both the facile addition of a very weak nucleophile, and its reversibility suggest a Michael addition with rather an unconventional mechanism. It has probably a low energy barrier and it involves a concerted mechanism associated with a neighboring group acid catalysis, as shown in Scheme I. The hydroxyl group is very acidic and tends also to form hydrogen bonds with various donors. At the same time the isoxazole ring which is electron deficient has a tendency to combine with π donors like the double bond in mesityl oxide. These properties probably enhance the approach of the reactants as shown in Scheme I, thus a concerted mechanism is made possible.

Scheme I



By studying the influence of the substituent X on the addition reaction it was found that the initial rate is accelerated by an electron attracting group and slowed down by electron donating groups. The dependency of the equilibrium constant of the addition reaction is attributed to the difference in the tautomeric structure in the various solvents. It has been shown (2), for instance, that in chloroform the predominant tautomer of **2** (X = H) has a saturated isoxazole ring, whereas in acetone it has not. The different tautomers have a characteristic pmr pattern

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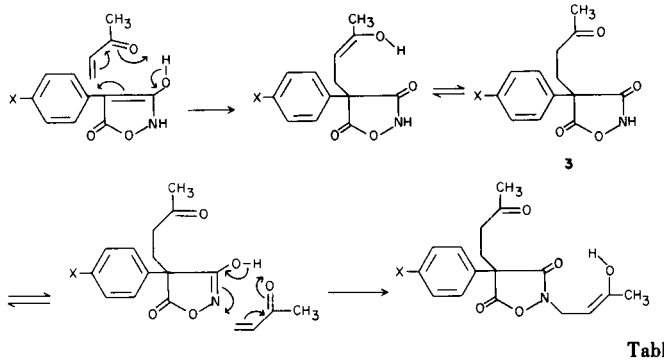
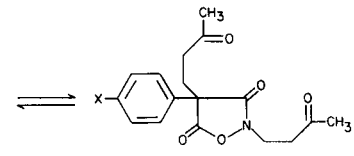
of the aromatic protons. In the case of 2-(1,1-dimethyl-3-oxobutyl)-4-(*p*-nitrophenyl)isoxazolidine-3,5-dione (**2**, X = NO_2) the aromatic protons show a single peak in THF and a distinctive AB system in DMSO.

The reason why the addition to mesityl oxide involves the nitrogen rather than the carbon at position 4 of the isoxazole ring is probably because of steric hindrance. The phenyl group is quite a large group that hinders the addition to the double bond at the carbon which is substituted with two methyl groups. Therefore, when phenyldisic acids (**1**) are exposed to methyl vinyl ketone which does not have these steric requirements, the first equivalent of methyl vinyl ketone reacts with the carbon at position 4 of the isoxazole ring. A second equivalent reacts with the nitrogen as shown in Scheme II. The reaction with methyl vinyl ketone is exothermic and irreversible. The mechanism of the reaction is similar to that with mesityl oxide but first it yields the thermodynamically more stable C-C bond. There is a possibility then to regain the proper tautomeric structure that leads to a second addition through the nitrogen.

Scheme II





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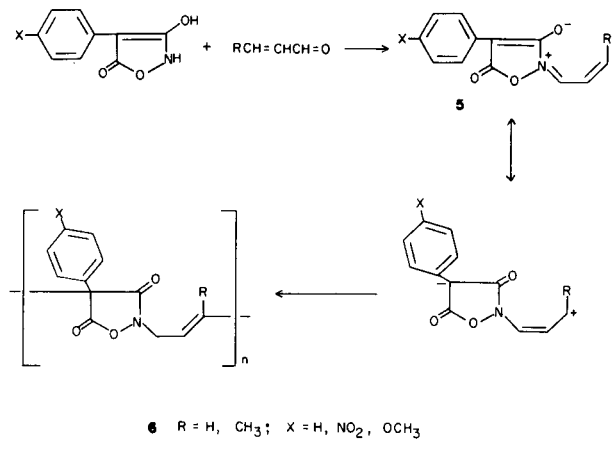
The side chain of the bis-Michael addition product (**4**) which is attached to the nitrogen is differentiated from that attached to the carbon by its pmr pattern. The first shows two distinctive triplets whereas the second shows a broad singlet of the two methylenic groups at a higher field. The attachment of a chain to the carbon at both position 4 of the isoxazole ring and the nitrogen causes the fixation of the saturated dione structure which is illustrated by the high frequency of the carbonyl absorption (1800 cm^{-1}) and by the pmr of the aromatic protons. The

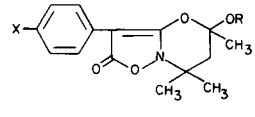
Scheme III



6 R = H, CH_3; X = H, NO_2, OCH_3

Table 1

Pmr Spectra of 5-Alkoxy-2-oxo-3-aryl-5,7,7-trimethyl-2*H*,7*H*-isoxazolo[3,2-*b*][1,3]oxazines (**7**)



R	X	Phenyl	6-CH_2	7-$C(CH_3)_2$	5-CH_3	OR
CH_3	H	7.2-7.4 (3H) 7.8-8.1 (2H)	2.30 bs	1.40 s	1.60 s	3.32 s
CH_3	OCH_3	6.9 d, 9.9 d	2.35 bs	1.45 s	1.50 s	3.25 s
CH_3	NO_2	8.1 s	2.40 s	1.51.s 1.46 s	1.80 s	3.40 s
CH_2CH_3	H	7.2-7.4 (3H) 7.8-8.0 (2H)	2.30 bs	1.48 s 1.40 s	1.68 s	3.62 q, 1.05 t
CH_2CH_3	OCH_3	6.9 d, 7.9 d	2.36 bs	1.50 s 1.48 s	1.70 s	3.70 q, 1.20 t
CH_2CH_3	NO_2	8.1 s	2.40 bs	1.60 s 1.50 s	1.80 s	3.75 dq, 1.10 t
$CH(CH_3)_2$	H	7.1-7.3 (3H) 7.7-8.0 (2H)	2.25 bs	1.45 s 1.37 s	1.65 s	4.23 h, 1.12 d, 0.90 d (J = 6 Hz)
$CH(CH_3)_2$	NO_2	8.15 s	2.42 bs	1.58 s 1.49 s	1.80 s	4.30 h, 1.30 d, 1.00 d (J = 7 Hz)

addition of methyl vinyl ketone is irreversible in DMSO or any other solvent and the products are also stable in acids or bases.

On the basis of the findings described above for the reaction of methyl vinyl ketone with phenyldisic acid and considering the high reactivity of the acids towards aldehydes (1,2) to form aldisates, it is possible now to assign a reasonable structure to the polymer which is obtained in the reaction of phenyldisic with acrolein or with crotonaldehyde (2). The course of reaction and the structure of the polymer (**6**) is shown in Scheme III. It is assumed that the first step is the condensation of the carbonyl group, followed by polymerization of the reactive α,β-unsaturated intermediate (**5**) via a Michael addition reaction through the carbon at position 4 of the isoxazole ring. In some cases the formation of this intermediate (**5**) is illustrated by temporary red coloration of the reaction mixture.

2-(1,1-Dimethyl-3-oxobutyl)-4-arylisoxazoline-3,5-diones (**2**) undergo facile ring closure in alcohols to 5-alkoxy-2-oxo-3-phenyl-5,7,7-trimethyl-2*H*,7*H*-isoxazolo[3,3-*b*][1,3]oxazines (**7**). In order to understand this spontaneous cyclization we have investigated various aspects of this reaction. The reaction was carried out in quartz cells (0.1 cm light path) and followed by taking the uv spectra at time intervals, at 25°. It was found that the fastest reaction occurred in methanol. The reaction in ethanol is slightly slower. In 2-propanol it is 4 times slower than in methanol. No cyclization occurs in *t*-butyl alcohol. The reaction of 2-(1,1-dimethyl-3-oxobutyl)-4-(*p*-methoxyphenyl)isoxazolidine-3,5-dione (**2** X = OCH_3) with ethanol is 30 times slower than the nitro derivative (**2**, X = NO_2). The methoxy derivative (**2**, X = OCH_3) reacts under the same conditions (25°) with 2-propanol too slow to be followed at all. In this case the decomposition of **2**, (X = OCH_3) to mesityl oxide and *p*-methoxyphenyldisic acid (**1**, X = OCH_3) competes with the cyclization reaction.

The cyclization reaction does not proceed in the presence of about 1 equivalent of water, so that when the reaction is carried out in low concentrations dry alchols had to be used. In wet alcohols the retro Michael elimination took place. The addition of sulfuric acid caused only a minor acceleration of the reaction as compared to the effect of a nitro group on the phenyl ring. Catalytic amounts of sulfuric acid gave an increase of the rate constant of 3 fold. A large excess of sulfuric acid gave not more than an increase of 8 fold.

The effect of the nitro group which is a strong electron withdrawing group on the cyclization reaction can be explained by an intramolecular acid catalyzed mechanism. Such a group will rather decrease the nucleophilicity of the attacking isoxazole ring; thus the enhancement of the reaction is probably by increasing the acidity of the heterocycle. Under basic conditions, *e.g.*, by trying to cyclize the di-*n*-butylammonium salt of **2** (X = H) no reaction occured. If the mechanism involved the attack of the enolate ion the salt would have cyclized readily. By considering the effect of both the type of alcohol and the kind of substituent X, it is assumed that the rate determining step in the cyclization reaction involves the alcohol or an

Scheme IV

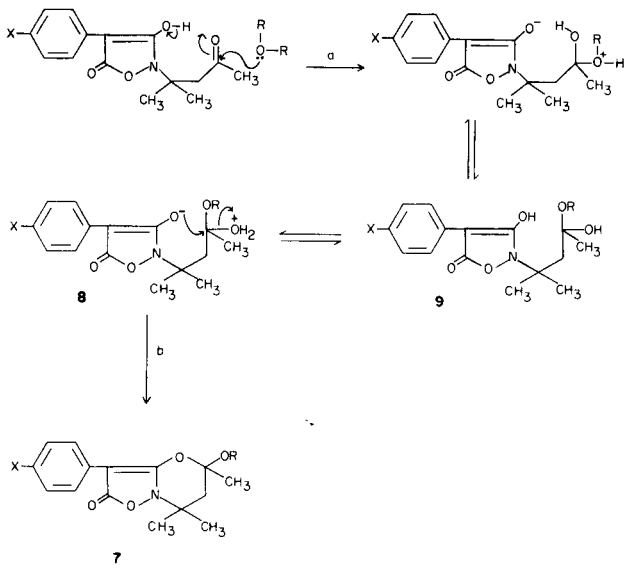


Table 2

Dissociation Constants and Spectral Data of 2-(1,1-Dimethyl-3-oxobutyl)isoxazolidin-3,5-diones (**2**)

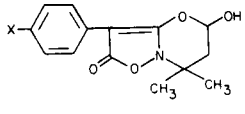
X	p*K*a	Ir (CO) cm^{-1}		Uv, λ max (ε × 10^3)		
		in chloroform	in DMSO	Neutral form	Anion	in Methanol (a)
H	10.4	1828 1725	1715	253 (22.3)	224 (16.5) 236 (14.4) 275 (12.2)	269 (13.2) 250 (sh)
NO_2	9.4	1825 1730	1700	388 (13.6)	236 (21.4) 438 (14.7)	242 (15.1) 385 (13.6)
OCH_3	10.6	1820 1725	1730	254 (22.9)	245 (19.8) 271 (sh)	250 (11.5) 278 (16.8)

(a) Anhydrous methanol was used. In wet solvent the spectra are different.

intermediate that contains the elements of the alcohol and is catalysed internally by the acidic hydroxyl group. The mechanism which is proposed for the cyclization of **2** to **7** is shown in Scheme IV.

It was shown by constructing a model that a branched R group would cause a considerable steric hindrance for cyclization. The equilibrium **9**⇌**8** is depending on the acidity of the hydroxyl group of the isoxazole ring. Therefore, it is most likely that step *b* is the rate determining step as it involves the carbon that contains the group R which comes from the alcohol and a tautomer, concentration of which is controlled by the acidity of the isoxazole moiety. However, if step *a* is concerted, as shown in Scheme IV, this step is not completely excluded from being the rate determining step.

There is no evidence for the formation of the hemiacetal **10**, neither from the kinetic nor by spectral study of this reaction. It is neither formed as an intermediate nor as a product in the absence of an alcohol. It is assumed that the reaction does not proceed in the presence of water because a hydrate is formed. The tautomeric structure of the latter is such that it prevents the ketalization by the mechanism which is described above. Structure **11** shows how water can stabilize a tautomer that will tend to decompose by a retro Michael reaction rather than cyclize by the addition of alcohol. The formation of another tautomer in the presence of water is evidenced by the change in the uv absorption.



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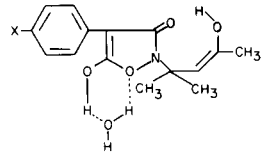

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The pmr spectra of the 5-alkoxy-2-oxo-3-phenyl-5,7,7-trimethyl-2*H*,7**H**-isoxazole[3,2-*b*][1,3]oxazines (**7**) exhibit some relevant findings:

i) *Aromatic protons:* The heterocyclic part of the molecule has a strong deshielding effect, comparable to that of a nitro group. Thus the four protons of the *p*-nitrophenyl derivative (**7**, X = NO_2) give a single peak. On the other hand the *p*-methoxy derivative (**7**, X = OCH_3) shows an AB system (very close to an AX system) for the four aromatic protons. ii) *The protons of the methyl groups at position 7:* The difference in the chemical shift between these two methyl groups depends both on the size of the alkoxy group at position 5 and on the substituent X on the phenyl group. The influence of X is somewhat surprising as it is so much away. It decreases from 0.15 cps in the 5-isopropoxy-3-(*p*-nitrophenyl)isoxazolooxazine derivative (**7**, R = $CH(CH_3)_2$, X = NO_2) to zero in the 5-methoxy-3-(*p*-methoxyphenyl)isoxazolooxazine derivative (**7**, R = CH_3, X = OCH_3), as shown in Table 1. iii) *The protons of the alkoxy group at position 5:* In all the 5-isopropoxy derivatives of **7** (R = $CH(CH_3)_2$, X = H, OCH_3, NO_2) the isopropyl group shows two doublets for the protons of its two methyl groups. The difference in chemical shift between the two doublets increases by going from X = OCH_3 to X = NO_2. The existence of two doublets in the isopropyl group indicates the prochirality of the bicyclic system. The two methyls of this group are therefore diasterotropic. In the 5-ethoxy-3-(*p*-nitrophenyl) derivative (**7**, R = CH_2CH_3, X = NO_2) the two methylenic protons of the ethoxy group give a double quartet, because they are diastereotropic protons as well.

EXPERIMENTAL

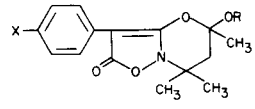
The nmr spectra were determined with a Varian T-60 spectrometer and TMS as internal reference. Uv and visible spectra were taken with a Varian Techtron spectrophotometer, Model 635. Ir spectra were taken with a Perkin Elmer Spectrophotometer, Model 237. Melting points are uncorrected. Unless stated otherwise, petroleum ether is of a boiling range 40-60°.

Diethyl α-Arylmalonates.

α-(*p*-Nitrophenyl)malonate was prepared by the substitution of *p*-nitrofluorobenzene with diethyl potassium malonate in *t*-butyl alcohol as

Table 3

Experimental Data for 5-Alkoxy-2-oxo-3-aryl-5,7,7-trimethyl-2*H*,7*H*-isoxazolo[3,2-*b*][1,3]oxazines (**7**).



R	X	Yield %	°C	Formula	Calcd. %C	Calcd. %H	Calcd. %N	Found %C	Found %H	Found %N
$CH(CH_3)_2$	H	81	144	$C_{16}H_{23}NO_4$	68.12	7.30	4.41	68.21	7.23	4.49
CH_3	NO_2	74	155	$C_{16}H_{18}N_2O_6$	57.48	5.43	8.38	57.52	5.56	8.40
CH_2CH_3	NO_2	80	135	$C_{17}H_{20}N_2O_6$	58.61	5.79	8.04	58.89	5.55	7.96
$CH_2CH_2CH_3$	NO_2	60	117	$C_{18}H_{22}N_2O_6$	59.66	6.12	7.73	59.54	5.92	7.69
$CH(CH_3)_2$	NO_2	50	133	$C_{18}H_{22}N_2O_6$	59.66	6.12	7.73	59.66	6.19	7.66
CH_3	OCH_3	72	128	$C_{17}H_{21}NO_5$	63.94	6.63	4.39	64.23	6.51	4.55
CH_2CH_3	OCH_3	51	151	$C_{18}H_{23}NO_5$	64.85	6.95	4.20	64.70	6.89	4.44

described earlier (4). Diethyl α-(*p*-methoxyphenyl)malonate was prepared by condensation of ethyl *p*-methoxy phenylacetate with diethyl carbonate, according to a procedure described earlier (4) with a slight modification. Good yields of the malonate were obtained when the neutralization of the reaction mixture with acetic acid was carried out prior to the evaporation in vacuum.

Table 4

Rate of Cyclization of 2-(1,1-Dimethyl-3-oxobutyl)isoxazolidine-3,5-diones (**2**) in Alcohols

X	Solvent	k (min^{-1})
NO_2	Methanol	6.0×10^{-2}
NO_2	Ethanol	4.6×10^{-2}
NO_2	Propanol	1.48×10^{-2}
OCH_3	Ethanol	1.5×10^{-3}
OCH_3	Ethanol + 1 equivalent of sulfuric acid	1.31×10^{-2}
OCH_3	Ethanol + traces of sulfuric acid	4.54×10^{-3}

Phenyldisic Acids.

These were synthesized from the corresponding malonates by procedures described earlier (1,5).

2-(1,1-Dimethyl-3-oxobutyl)-4-(*p*-methoxyphenyl)isoxazolidine-3,5-dione (**2**, X = OCH_3).

(*p*-Methoxyphenyl)disic acid (**1**, X = OCH_3) (1.03 g.) was heated to boiling in mesityl oxide (4 ml.). Cooled overnight at −10° while crystallization occured. A mixture of ether-petroleum ether (1:2) was added in order to complete the precipitation. The precipitate was collected and washed with petroleum ether. The product was pure without recrystallization (0.83 g., 55%), m.p. 109° p*K*a = 10.6. Spectral data are given in Table 2.

Anal. Calcd. for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.65; H, 6.35; N, 4.44.

Following the Addition of Phenyldisic Acids to Mesityl Oxide. a) In DMSO-d_6.

A phenyldisic acid (**1**) (1×10^{-4}) was dissolved in DMSO-d_6 (0.6 ml.) in an nmr tube and mesityl oxide (0.01 ml., about 1×10^{-4} mole) was added. Nmr spectra were run at intervals of 5 minutes. At the end of the reaction spectra were run every 30 minutes.

b) In THF.

A solution of phenyldisic acid (**1**) (1×10^{-3} mole) was prepared in THF (5 ml.). Aliquots of this solution (0.6 ml.) were mixed with mesityl oxide (0.01 ml.) in an nmr tube and the spectra were taken at intervals as above. When the THF was not a deuterated solvent the progress of the reaction could be followed by the change in integration of the vinylic proton and also by the change in the chemical shift of the exchangeable protons.

Following the Course of Decomposition of 2-(1,1-Dimethyl-3-oxobutyl)-4-arylisoxazolidine-3,5-diones (**2**) in DMSO-d_6.

The addition products (**2**) (1×10^{-4} mole) was dissolved in DMSO-d_6 (0.6 ml.) and the pmr spectra were taken at intervals as above for the formation of **2**. The equilibrium constants were determined from the concentrations at the end of the reaction. These constants were about the same for the *p*-methoxy derivative (**2**, X = OCH_3) and the unsubstituted one (**2**, X = H); K = 1.8 $mole^{-1}$. For the nitro derivative (**2**, X = NO_2) it was smaller: K = 0.36 $mole^{-1}$.

Determination of the Acidic Dissociation Constant of 2-(1,1-Dimethyl-3-oxobutyl)-4-arylisoxazolidine-3,5-diones (**2**).

Compound **2** (5 mg.) was dissolved in a solution of 0.1*M* disodium hydrogen phosphate + 0.06 *N* sodium hydroxide (25 ml.). Five ml. of this solution was dissolved in 0.02 *N* hydrochloric acid (5 ml.) (solution A). Another sample of 5 ml. was diluted to 50 ml. with water (solution B). The p*H* was adjusted by mixing solutions A and B in different proportions. The uv spectra were taken at intervals of 0.3 p*H* units against references prepared in a similar way. The p*K*a was calculated from the formula:

$$pKa = pH_1 + \log \frac{\epsilon_{A^-} - \epsilon_1}{\epsilon_1 - \epsilon_{AH}}$$

where ϵ_1 is the extinction coefficient at a certain pH_1 and the ϵ_{A^-} and ϵ_{AH} are the extinction coefficients of the anion and the neutral molecule respectively. The p*K*a's are given in Table 2.

2,4-Bis(3-oxobutyl)-4-phenylisoxazolidine-3,5-dione (**4**, X = H).

Phenyldisic acid (0.5 g.) is dissolved in methyl vinyl ketone (2 ml.). Excess of the methyl vinyl ketone is evaporated in vacuum. The product is washed with a solution of sodium bicarbonate and extracted with ether. The etheral layer dried (sodium sulfate) and evaporated to dryness. The product is an oil (0.84 g., 98%); pmr (deuteriochloroform): δ 2.15 s (4-$COCH_3$), 2.22 s (2-$COCH_3$); 2.60 bs (4-CH_2CH_2), 2.91 t (N-CH_2), 4.10 t (N-C-CH_2CO), 7.37-7.7 (C_6H_5).

Molecular weight: Calculated for $C_{17}H_{19}O_5N$: 317. Found by ms: m/e 317.

Anal. Calcd. for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03; N, 4.41. Found: C, 64.61; H, 5.99; N, 4.36.

4-(3-Oxobutyl)-4-phenylisoxazolidine-3,5-dione (**3**).

Methyl vinyl ketone (0.7 g.) in THF (5 ml.) was added to phenyldisic acid (1 X = H) (1.77 g.) and the solution stirred at room temperature for 10 minutes. The residue was dissolved in ether (50 ml.), washed with a solution of 5% bicarbonate, dried (sodium sulfate), and evaporated in vacuum. The residue consisted of the bis adduct (**4**), 0.46 g. The aqueous layer was brought to p*H* 3.4 and extracted with 3 portions (30 ml.) of ether. The ether was dried in (magnesium sulfate) and evaporated to dryness. The mono adduct (**3**) is an oil (1.2 g., 50%). The aqueous solution contained more of **3** and unchanged starting material (**1**); nmr (deuteriochloroform): δ 2.15 s (4-$COCH_3$), 2.60 bs (4-CH_2CH_2), 7.3-7.7 (C_6H_5).

Molecular weight: Calculated for $C_{13}H_{13}NO_4$: 247. Found by ms m/e 247.

Anal. Calcd. for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.31; N, 5.66. Found: C, 63.08; H, 5.61; N, 5.58.

5-Alkoxy-2-oxo-3-(*p*-nitrophenyl)-5,7,7-trimethyl-2*H*,7*H*-isoxazolo[3,2-*b*]-[1,3]oxazines (**7**, X = NO_2).

2-(1,1-Dimethyl-3-oxobutyl)-4-(*p*-nitrophenyl)isoxazolidine-3,5-dione (**2**, X = NO_2) was boiled in an alcohol. Compound **2** in methanol for 2 minutes gave **7** (R = CH_3, X = NO_2). In ethanol for 5 minutes **2** gave (R = CH_2CH_3, X = NO_2). In 1-propanol for 15 minutes, **2** gave **7** (R = $CH_2CH_2CH_3$, X = NO_2). When **2** was allowed to react in 2-propanol for 20 minutes, **7** (R = $CH(CH_3)_2$, X = NO_2) was obtained. The analytical results are summarized in Table 3.

5-Alkoxy-2-oxo-3-phenyl-5,7,7-trimethyl-2*H*,7*H*-isoxazolo[3,2-*b*][1,3]oxazines **7** (X = H).

The products where R = CH_3 and R = CH_2CH_3 were previously reported (2). The isopropyl derivative **7** (R = $CH(CH_3)_2$, X = H) was prepared by boiling 2-(1,1-dimethyl-3-oxobutyl)-4-phenylisoxazolidine-3,5-dione (**2**, X = H) (0.2 g.) in 2-propanol (4 ml.) for 90 minutes. The solution was kept overnight at −10°. The product which precipitated was collected and then recrystallized from ether. The results are summarized in Table 3.

5-Alkoxy-2-oxo-3-(*p*-methoxyphenyl)-5,7,7-trimethyl-2*H*,7*H*-isoxazolo-[3,2-*b*][1,3]oxazines (**7**, X = OCH_3).

2-(1,1-Dimethyl-3-oxobutyl)-4-(*p*-methoxyphenyl)isoxazolidine-3,5-dione (**2**, X = OCH_3) (0.5 g.) was dissolved in either methanol or ethanol (5 ml.) and kept for a week at room temperature. The products (**7**, X = OCH_3, R = CH_3 or CH_2CH_3) crystallized in a pure form. Reaction in propanol lead only to a small yield of the isopropoxy derivative **7** (X = OCH_3, R = $CH(CH_3)_2$) which could not be purified. The results are summarized in Table 3.

Di-*n*-butylammonium Salt of 2-(1,1-Dimethyl-3-oxobutyl)-4-phenylisoxazolidine-3,5-dione.

2-(1,1-Dimethyl-3-oxobutyl)-4-isoxazolidine-3,5-dione (**2**, X = H) (0.5 g.) was dissolved in di-*n*-butylamine (10 ml.) and stirred at room temperature. The solution became clear and after 10 minutes the precipitated salt was collected, washed with petroleum ether and recrystallized from cyclohexane (0.5 g., 60%), m.p. 84°.

Anal. Calcd. for $C_{23}H_{36}N_2O_4$: C, 68.29; H, 8.97; N, 6.92. Found: C, 67.57; H, 8.83; N, 6.93.

This product does not undergo any change on boiling in alcohols.

Determination of the Rate of Formation of 5-Alkoxy-2-oxo-3-aryl-5,7,7-trimethyl-2*H*,7*H*-isoxazolo[3,2-*b*][1,3]oxazines (**7**).

2-(1,1-Dimethyl-3-oxobutyl-4-arylisoxazolidine-3,5-diones (**2**) (2 mg., $\sim 6 \times 10^{-6}$ mole) were dissolved in 100% alcohol (5 ml.). The uv and visible spectra were taken at intervals in cells of 0.1 cm optical path. The intervals ranged from 5 minutes for the nitro derivative to 4 hours for the methoxy derivative. When the effect of sulfuric acid was studied, 0.01 ml. of 10% ethanolic sulfuric acid was added to the reaction mixture. When studying the effect of traces of this acid, 0.01 ml. of 1% ethanolic sulfuric acid was added and the spectra taken every 30 minutes. A graph of $\ln(OD_\infty - OD)$ was plotted against time (t) and the first order rate constant (k) was determined from the slope. The rate constants are summarized in Table 4.

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