Geometric Isomers of 2-Aryl(Aralkyl)-4-arylidene(alkylidene)-5(4*H*)-oxazolones

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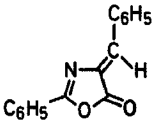
The chemistry of geometric isomers of 4-arylidene(alkylidene)-5(4*H*)-oxazolones with reference to methods for their preparation, their physical and chemical properties, and configurational assignments is discussed.

Die Chemie der geometrischen Isomeren von 4-Aryliden(Alkyliden)-5(4*H*)-oxazolone wird erörtert. Ihre Herstellungsmethoden, physikalischen und chemischen Eigenschaften und die Bestimmung ihrer Konfigurationen werden abgehandelt.

1. Scope of the Review

The chemistry of 5(4*H*)-oxazolones has been the subject of several reviews[1-6]. The isolation of geometric isomers of several 4-alkylidene(arylidene)-oxazolones has been reported, and a brief mention of these compounds has been made[1-6]. Among the known geometric isomers, structural assignments based on comparison with model compounds, pK_a measurements, and N.M.R. spectra have been made to the isomers of 2-phenyl-4-benzylidene-5(4*H*)-oxazolone[7,8,9] (**1**, **2**); 2-phenyl-4-(3′,4′-dimethoxybenzylidene)-5(4*H*)-oxazolone[10] (**3**, **4**); 2-phenyl-4-(2-pyrrolylidene)-5(4*H*)-oxazolone (**5**, **6**); and 2-phenyl-4-(2-acetoxy-1-methylethylidene)-5(4*H*)-oxazolone[11] (**7**, **8**).



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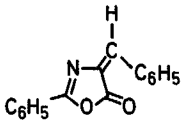

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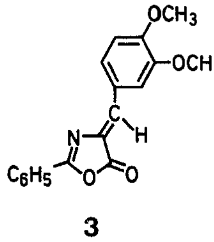

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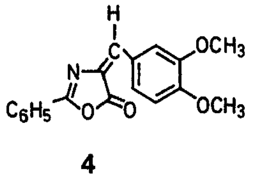

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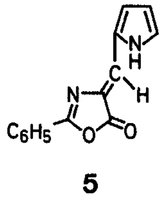

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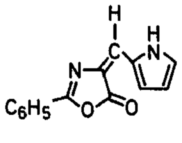

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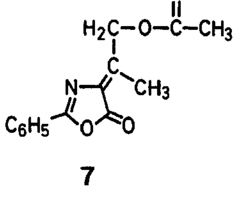

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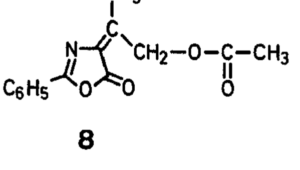

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A complete survey of these compounds and their chemistry will be included in this review.

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* Author to whom enquiries about this paper should be made.

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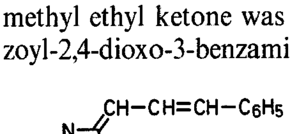
2. Introduction

Although the stable isomer—2-phenyl-4-benzylidene-5(4*H*)-oxazolone (**1**)—"Plöchl-Erlenmeyer" azlactone[12, 13]—has been known for a long time, its geometric isomer was not reported until 1941. The possibility of the existence of geometric isomers was indicated for 2-phenyl-4-cinnamylidene-5(4*H*)-oxazolone (**9**)[14] but the isomers were not isolated. The first set of isomers to be separated and characterized were those of 2-phenyl-4-ethylidene-5(4*H*)-oxazolone (**10**)[15, 16]. A similar occurrence of isomers **1** and **2** and their isolation was also reported[16]. It was also indicated[14, 15, 16] that the labile or the less common isomer could be converted to the more stable or common isomer by the action of pyridine. The reaction of 2-phenyl-4-ethoxymethylene-5(4*H*)-oxazolone (**11**) with various amino compounds, such as aniline, hydrazine, guanidine, and acetamidine was reported to yield geometric isomers[18]. The reaction of hippuric acid with 2-pyrrolecarbaldehyde[19], 2,6-dimethoxybenzaldehyde[20], ethyl orthoformate[21, 22], and methyl ethyl ketone[23, 24, 25] was also reported to give mixtures of geometric isomers. It may be pointed out that the reaction of hippuric acid and methyl ethyl ketone was reported[26] to give *N*-benzoyl-2,4-dioxo-3-benzamidopyrrolidine (**12**).



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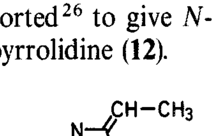

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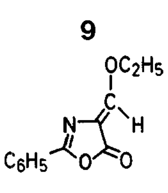

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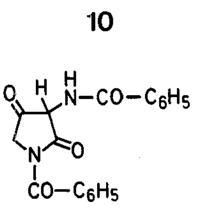

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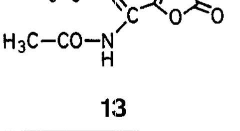
3. Methods of Preparation of Geometric Isomers

3.1. Fractional Crystallization of Azlactones Prepared under Perkin-Erlenmeyer Conditions (Method A)

When aldehydes are condensed with hippuric acid in the presence of acetic anhydride and sodium acetate, usually one isomer of an azlactone is obtained. In the case of a few aldehydes, a mixture of geometric isomers of the oxazolone is obtained. Thus, cinnamaldehyde gives a crude mixture of isomers melting at 118–136°[14]. The mixture is not separated but hydrolyzed by alkali and the acid is recyclized to give **9** (m.p. 152°). Reactions of pyrrole-2-carbaldehyde[19] and 2,6-dimethoxybenzaldehyde[20] also give mixtures of isomeric oxazolones. The choice method of separation of the isomers seems to be crystallization from 95% ethanol. Usually the less soluble isomer crystallizes out while the mother liquor yields the more soluble isomer[20]. In the case of 2-phenyl-4-*sec*-butylidene-5(4*H*)-oxazolone, the crude mixture is hydrolyzed with an amount of alkali less than that theoretically required. Only a portion of the oxazolone goes into solution while the rest remains unaffected. This alkali insoluble portion is recrystallized from 70% alcohol to give the isomer melting at 63–64°. The alkaline solution is acidified and the precipitated acid cyclized with acetic anhydride to give the second isomer melting at 52–54°[22]. Crystallization from isopropyl alcohol also causes separation of the isomers sometimes[11, 32].

An alternate method seems to be dilution of the mother liquor with water after removal of one isomer[27]. Thus, the two geometric isomers of 2-β-[β-acetamidostyryl]-4-benzylidene-5(4*H*)-oxazolone (**13**) have been separated[27]. Recently Merchant and Shetty reported the syntheses of pairs of geometric isomers from xylenol aldehydes[87, 88, 89]. These isomers are separated by their differential solubilities in benzene. Biacetyl is reported to condense with hippuric acid to give two isomers[95].



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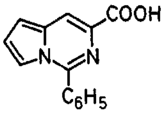
In the case of pyrrole-2-carbaldehyde[19], the oxazolone mixture, on recrystallization from benzene gives the isomer melting at 173° while the mother liquor gives a mixture of the two isomers, which are separated by alkaline hydrolysis to the α-benzamido-β-(2-pyrrole)-acrylic acids, and recyclization with acetic anhydride to give the isomer melting at 186°. Alkaline hydrolysis also gives 4-phenylpyrrolo[1,2-*c*]pyrimidine-2-carboxylic acid (**14**) easily obtainable from **6** but not from **5**. This fixes the configurations of the two isomers.



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When *o*-anisaldehyde is condensed with hippuric acid, 2-phenyl-4-*o*-anisylidene-5(4*H*)-oxazolone (m.p. 164°) is obtained[28, 29, 30]. Under essentially similar conditions, an oxazolone with melting point 154° has also been obtained[31]. An oxazolone with a similar melting point has also been reported[47]. The two isomers have been prepared later and shown to be interconvertible[28, 31].

3.2. Isomerization in Saturated Hydrobromic Acid (Method B)

When 2-phenyl-4-benzylidene-5(4*H*)-oxazolone (**1**), is suspended in 48% hydrobromic acid and the acid is then saturated with hydrogen bromide, isomerization occurs to give **2** in near quantitative yields[34]. This method has been employed in the isomerization of several azlactones[10, 33, 34, 35]. The azlactones obtained from *p*-tolualdehyde and anisaldehyde failed to isomerize under these conditions[30]. This conclusion is based on a comparison of melting points. It is quite likely that the isomerization had taken place in both these cases and the melting points of the isomers are quite close to those of the starting materials, as in the case of **3** and **4**[10].

Preparation of 2 (Geometric Isomer of 1):

A suspension of **1** (5 g) in 48% hydrobromic acid (90 ml) was put in a 250 ml Erlenmeyer flask. The flask was cooled in an ice bath and its contents were saturated with anhydrous hydrogen bromide gas for 0.5 h. During this time, the temperature was kept at 0° (it should not exceed 50°, in any case). The flask was left in a refrigerator overnight. The contents were poured on crushed ice, the solid azlactone was filtered, washed free of acid with water, and dried. It was then recrystallized from benzene; yield: 97%; m.p. 148.5°.

This is the choice method for preparing geometric isomers since the reaction nearly always gives the desired isomer.

3.3. Tertiary Amine Catalyzed Isomerization (Method C)

This method is strictly for converting the labile isomer to the stable one and consists mainly of treating the former with pyridine at room temperature for 15 min[11, 12]. This method, with slight variations, has been employed for many azlactone isomerizations[14, 15, 22, 24, 25].

Isomerization of 2 to 1:

A sample of 2-phenyl-4-benzylidene-5(4*H*)-oxazolone (**2**; 0.3 g) was dissolved in pyridine (3 ml) at room temperature. After 3 minutes, the solution was poured into an excess of hydrochloric acid on crushed ice. The precipitated azlactone was mainly **1**; yield: 100%; m.p. 166°.

3.4. Photo-Induced Isomerization (Method D)

When a solution of 2-phenyl-4-benzylidene-5(4*H*)-oxazolone (**1**) in degassed isopropyl alcohol is irradiated with 3650 Å light, isomerization occurs with the formation of **2**[36, 38, 91]. With light of wavelength 2537 Å, the only product obtained is 3-benzamido-4-phenyl-3,3-dimethylbutyrolactone formed possibly via the postulated intermediate, 1,1-dimethyl-2-phenyl-2-(1-phenyl-5-hydroxy-4-oxazolyl)-ethanol. Increasing the concentration of the azlactone in alcohol only reduces the rate of butyrolactone formation while the rate of isomerization remains unchanged. The geometric isomer **2** is prepared by the irradiation of **1** in tetrahydrofuran or isopropyl alcohol for 90 minutes. Chromatographic separation gives a 45% yield of **2**.

When **2** dissolved in acetonitrile is left at room temperature in light for a few days, isomerization to an equilibrium point appears to be reached (60% *trans*-40% *cis*). In the dark the product is exclusively the *trans* isomer. The photo-*trans* isomer thus obtained, reverts back to 60:40 equilibrium mixture in light, a property which is not shown by the Plöchl-Erlenmeyer azlactone **1**[9].

The isomerization of 2-phenyl-4-(2′-acetoxybenzylidene)-5(4*H*)-oxazolone in degassed isopropyl alcohol to the labile form in 18% yield has been reported recently[39]. In the conversion of 2-phenyl-4-(2′-hydroxy-5′-methylbenzylidene)-5(4*H*)-oxazolone to 3-benzamido-6-methylcoumarin by photo-chemical methods, isomerization of the oxazolone has been postulated to occur before the coumarin formation[40]. Similar conversion of salicylidene azlactone to 3-benzamidocoumarin has been reported[98].

3.5. Treatment of 4-Ethoxymethylene-2-phenyl-5(4*H*)-oxazolone (11) with Amines (Method E)

When compound **11** is treated with amines such as aniline, hydrazine, guanidine, and acetamidine, the corresponding anilino, hydrazino, guanidino, and acetamidinooxazolones are obtained as a mixture of two isomers. For liquid amines, the reaction procedure consists of shaking **11** with the amine while for solid amines, a strong alcoholic solution of the

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amines is employed. Some of these isomeric compounds have identical absorption spectra and melting points but seem to differ in their colors[18]. Similar observations are made about 2-phenyl-4-(1′-*p*-nitrophenylethylidene)-5(4*H*)-oxazolone[25] and 2-phenyl-4-(3-indolylmethylene)-5(4*H*)-oxazolone[100]. A recent report[41] about the reaction of benzylamine with **11** gives the less stable 2-phenyl-4-(1-benzylaminoethylidene)-5(4*H*)-oxazolone, while the stable isomer is obtained from 2-phenyl-4-[1-(2-hippuroylaminoethylthio)-ethylidene]-5(4*H*)-oxazolone.

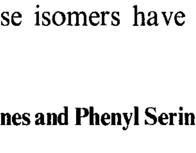
The compound 2-benzyl-4-methoxymethylene-5(4*H*)-oxazolone is reported to exist in two forms[18] but the properties of these isomers have not been enumerated.

3.6. From Substituted Threonines and Phenyl Serines (Method F)

When *N*-benzoyl-*dl*-threonine (**15**) or *N*-benzoyl-*dl*-allothreonine is treated with benzoyl chloride in pyridine, the stable isomer of **10** is obtained[15]. The *O*-acetyl or *O*-benzoyl or *O*-methyl derivatives also give **10** under identical conditions. Acetic anhydride may be used instead of benzoyl chloride.

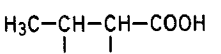
$H_3C-\underset{OH}{CH}-\underset{NH-CO-C_6H_5}{CH}-COOH$

15



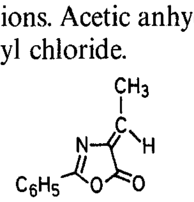
10 a

When *N*-benzoyl-*O*-methyl-*dl*-allothreonine (**16**) is heated with acetic anhydride for 15 min on a steam bath, the higher melting isomer **10b** is obtained in 30–35% yield[16].



$H_3C-\underset{H_3CO}{CH}-\underset{NH-CO-C_6H_5}{CH}-COOH$

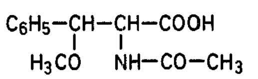
16



10 b

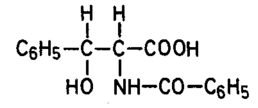
Work up of the mother liquor gives a 45–50% yield of **10a**. On treatment with aqueous acetic acid and sodium acetate, compound **16** gives a mixture of **10a** and **10b**. The structural assignments for **10a** and **10b** are based on the tendency of **10b** to be isomerized to **10a** on heating. However Brown and Smale[82] reported that **10a** gave methyl α-benzamidocrotonate on hydrolysis and that the latter compound has *cis* configuration based on N.M.R. evidence. They thus assigned structure **10b** for the isomer melting at 91° and it follows that **10a** is the structure for the higher melting isomer.

When *dl*-*O*-methyl-*N*-benzoylphenylserine[7, 42] (**17**) is heated with acetic anhydride, compound **1** crystallizes out. Work up of the mother liquor gives a mixture of **1** and **2**, which are separated by way of the corresponding benzamidocinnamic acids. When **17** is treated with benzoyl chloride or acetic anhydride in pyridine, only **1** is obtained[17].



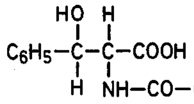
$C_6H_5-\underset{H_3CO}{CH}-\underset{NH-CO-CH_3}{CH}-COOH$

17



$C_6H_5-\overset{H}{\underset{HO}{C}}-\overset{H}{\underset{NH-CO-C_6H_5}{C}}-COOH$

18



$C_6H_5-\overset{HO}{\underset{H}{C}}-\overset{H}{\underset{NH-CO-C_6H_5}{C}}-COOH$

19

In a more recent method[8], *erythro* and *threo*-*N*-benzoyl-*β*-phenylserines (**18**) and (**19**) have been prepared and cyclized by treatment with acetic anhydride. Reaction of compound **18** with acetic anhydride gives a mixture of **1** and **2**. The *threo* compound **19** reacts to give **1** only.

Preparation of 2 from *O*-methyl-*N*-benzoylphenylserine:
Compound **17** (15 g), suspended in acetic anhydride (75 ml), was heated on a steam bath for 10–15 min. On cooling, compound **1** separated and was filtered. The filtrate, on pouring into ice water, gave solid **2** which was recrystallized from benzene/alcohol; yield: 4.6 g; m.p. 124–140°. Alcoholysis of **2** in benzene and 1*N* sodium ethoxide (10 ml) gave two crops of ester corresponding to **1**. After the removal of these two crops, the remaining oily material solidified to give ester corresponding to **2**. The ethyl ester was hydrolyzed in alcoholic sodium hydroxide to give α-benzamidocinnamic acid; m.p. 199–200°. This compound, on heating with acetic anhydride, gave **2**; m.p. 146–148°.

The above method is of little synthetic value since the discovery of hydrobromic acid catalyzed isomerization of **1**.

3.7. Sulfuric Acid Catalyzed Condensations (Method G)

When the condensation of benzaldehyde with hippuric acid is carried out in sulfuric acid/acetic anhydride mixture or 100% sulfuric acid, a mixture of **1** and **2** is obtained. It has been suggested that sulfuric acid inhibits the mutarotation of the intermediate 2-phenyl-4-(α-hydroxybenzyl)-5(4*H*)-oxazolone (**20**) which exists as a mixture of diastereomers.

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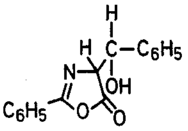


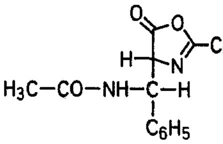
20

The *threo* pair, by *trans* elimination, would give **1** while the *erythro* pair would give **2**, thereby giving a mixture of isomers—an equimolar one in the absence of mutarotation and on the assumption of equal rates of elimination. Concentrated sulfuric acid has been shown to cause little or no isomerization of **1** and **2**[43, 44].

Recently, the first stereospecific synthesis of **2** has been reported. Although the yields are low, only **2** has been obtained from reaction of 2-phenyl-5(4*H*)-oxazolonium perchlorate and benzaldehyde[45, 94].

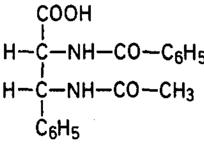
3.8. Special Methods (Method H)

When benzylidenebis-acetamide, obtained from benzaldehyde and acetamide[46], is condensed with hippuric acid in the presence of acetic acid/acetic anhydride mixture, it gives compounds **1**, **21**, and **22**[47].



21

threo-2-phenyl-4-(α-acetamidobenzyl)-5(4*H*)-oxazolone



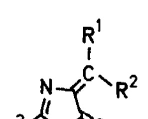
22

erythro-3-acetoamido-2-benzamido-3-phenylpropanoic acid

Compound **21** gives **1** by *trans*-elimination, while **22** on heating gives the *erythro* isomer of **21**. This *erythro* isomer, on further heating with acetic anhydride, is shown to give **2**[30]. It has been pointed out[44] that the structural assignments for the unsaturated oxazolones obtained by heating **21** and its *erythro* isomer have been incorrectly made. Thus reaction of the *threo* compound should give **1** and the *erythro* compound **2**.

Under similar conditions, the product obtained from *o*-anisylidenebis-acetamide is the lower melting isomer. (See Table 1.)

Table 1. Geometric Isomers of 4-Arylidene (Alkylidene)-5(4*H*)-oxazolones



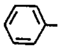
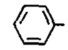
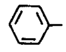
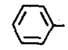
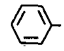
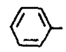
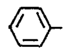
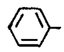
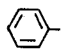
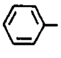
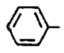
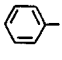
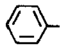
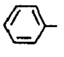
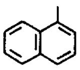
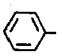
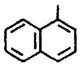
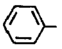
R¹	R²	R³	Yield (%)	Melting Point	Method of Preparation	Reference
	H		85–95(A)	166–167°*	A, C, D, G	—
H			97(B)	148–149°*	B, D, G	—
H_3C	H		—	95–96°	F	15
H	H_3C		—	144–145°	F	16
H_3C	C_2H_5O		—	112–113°	A	21, 22
C_2H_5O	H_3C		—	136–138°	A	21, 22
H_3C	C_2H_5		70	52–54°	A	23, 24
C_2H_5	CH_3		—	63–64°	A	23, 24
–CH=CH–	H		—	152°, 167°	A	14, 101
H	–CH=CH–		10	143°	A	32
	H		—	186°	A	19
H			—	173°	A	19
	H		50, 100	170°	A, C	30, 33
H			70	160°	B	30, 33

Table 1. (continued)

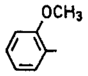
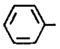
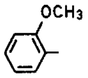
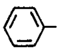
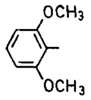
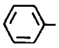
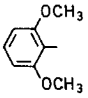
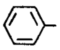
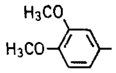
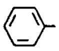
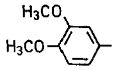
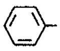
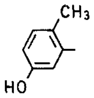
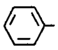
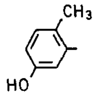
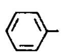
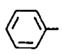
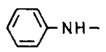
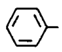
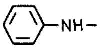
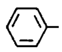
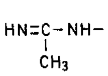
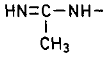
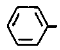
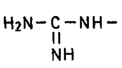
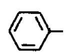
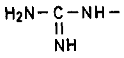
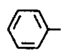
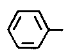
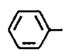
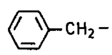
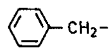
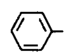
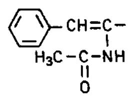
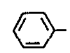
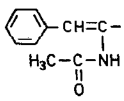
R¹	R²	R³	Yield (%)	Melting Point	Method of Preparation	Reference
	H		70–80	166°	A, C	28, 29, 30
H			68	156°	B	30, 31, 33, 47
	H		50	121°	A, C	20
H			10, 67	167°	A, B	20, 30, 33
	H		69–73	147.5–148.5°	A, C	10
H			50	141–142°	B	10
	H		—		D	40
H			—	—	D	40
$H_2N{-}NH{-}$	H		—	—	E	18
H	$H_2N{-}NH{-}$		—		E	18
	H		—	Mixture of two isomers	E	18
H			—	M.p. difference 30°	E	18
 $HN{=}\underset{CH_3}{\underset{\vert}{C}}{-}NH{-}$	H		—	144° (Red)	E	18
H	 $HN{=}\underset{CH_3}{\underset{\vert}{C}}{-}NH{-}$		—	144° (Yellow)	E	18
 $H_2N{-}\underset{NH}{\underset{\Vert}{C}}{-}NH{-}$	H		—	214° (Red)	E	18
H	 $H_2N{-}\underset{NH}{\underset{\Vert}{C}}{-}NH{-}$		—	214° (Yellow)	E	18
H_3C	$H_3C{-}COO{-}CH_2{-}$		22	101–102°	A	11
$H_3C{-}COO{-}CH_2{-}$	H_3C		10	81–82°	A	11
H_3CO	H			—	A	18
H	H_3CO		—	—	A	18
	H		—	184–186°	A	27
H			—	191–193°	A	27

Table 1. (continued)

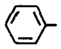
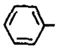
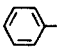
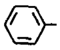
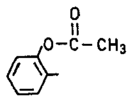
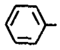
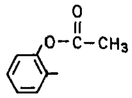
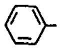
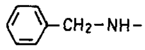
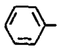
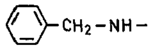
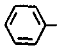
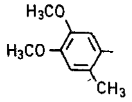
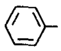
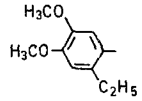
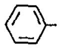
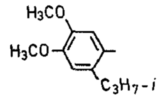
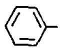
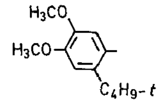
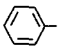
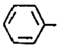
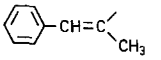
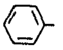
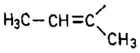
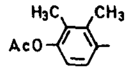
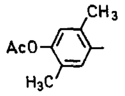
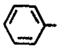
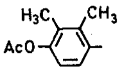
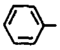
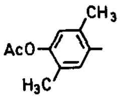
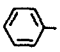
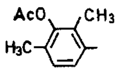
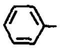
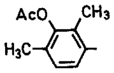
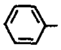
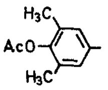
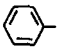
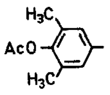
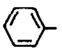
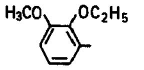
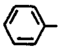
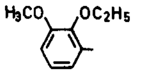
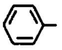
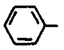
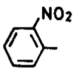
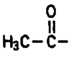
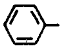
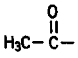
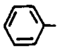
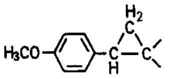
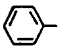
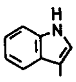
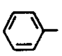
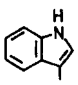
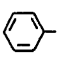
R^1	R^2	R^3	Yield (%)	Melting Point	Method of Preparation	Reference
	D		73	166°	A	35, 79, 80
D			—	148°	B	35
	H		7	138°	A	14b, 39
H			18	124°	D	39
H_3C			—	236–238°	E	41
	H_3C		30	127–129°	E	41
	H		72	168–169.5°	A	10b, 10c, 85
	H		57	155–157°	A	10b, 10c, 86
	H		53	162–164°	A	10b, 10c
	H		10	160–161°	A, D	10b, 10c
	H		44, 62	120–121°	A	83, 84
	H		93	115–116°	A	83, 84
	H		—	230°	A	87, 88
	H		—	225°	A	87
H			—	159°	A	87
H			—	165°	A	87
	H		—	212°	A	87
H			—	188°	A	87
	H		—	192°	A	87
H			—	188°	A	87

Table 1. (continued)

R^1	R^2	R^3	Yield (%)	Melting Point	Method of Preparation	Reference
	H		—	172°	A	87
H			—	140°	A	89
	H		30	151°	A	92
 $H_3C-C(=O)-$	CH_3		33	143.5–145°	A	95
CH_3	 $H_3C-C(=O)-$		4	87–88°	A	95
	*(cis)*		—	124°	A	96, 97
	(trans)		53	137°	A	96, 97
	H		56	220°	polyphosphoric acid method	99, 100
H			60	204°	E	99

4. Mechanism of Isomerization

As mentioned earlier, isomerization of compounds **1** and **2** occurs in 48% hydrobromic acid saturated with hydrogen bromide. It has been established that this isomerization proceeds in the presence of a radical initiator. Evidence that this procedure involves the generation and participation of bromine free radicals is supported by the following observations. Isomerization did not occur in the absence of light. In the presence of benzoyl peroxide, isomerization proceeded readily. When hydroquinone, a radical inhibitor, was present, isomerization did not occur. Also isomerization seems to proceed best when the temperature of the medium is kept below 50°. A carbonium ion intermediate is ruled out by these results and by the specificity of hydrogen bromide. *p*-Toluenesulfonic acid failed to cause isomerization of **1** to **2** while hydrogen chloride caused ring fission[48]. Concentrated sulfuric acid (100%) fails to isomerize **1** to **2**. A mechanism similar to the conversion of *cis*-stilbene to *trans*-stilbene[49] seems to be in order for this isomerization reaction.

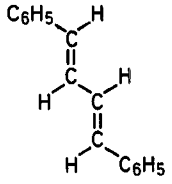
5. Differences in Isomer Properties

5.1. Physical Properties

It must be borne in mind that differences in physical properties refer to those of the parent oxazolones as well as the products of hydrolysis (α-benzamidoacrylic acids) and alcoholysis (esters of α-benzamidoacrylic acids). The assumption implicit in these studies is that configurational integrity is maintained during the hydrolysis and alcoholysis of these oxazolones.

5.1.1. U.V. Spectra

The ultraviolet absorption maxima and extinction coefficients for azlactones, benzamido acids derived from them, and the corresponding esters are given in Table 2. There does not seem to be any correlation between the spectra and geometric isomerism. The U.V. spectra for **1** and **2** were supposed to differ in the intensities of both 360 nm and 260 nm bands[7]. A more recent discussion of these spectra[9] indicates that the differences between the two spectra are in the intensities of the fine structure maxima in the short wavelength band and in the fine structure content of the long wavelength band. It is also pointed out that the spectrum of **1** is similar to that of *trans-trans*-1,4-diphenylbutadiene (**23**).



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There seems to be a shift towards longer wavelengths in the spectra of the acid and the ethyl ester derived from **2**, in comparison with those derived from **1**. In the case of the 2-phenyl-4-*s*-butylidene-5(4*H*)-oxazolone[21, 22] isomers, the low melting isomer has been reported to have absorption maxima at 310 and 290 nm while the other has maxima at higher wavelengths but with very much lower extinction coefficients. Similar observations have been reported for 2-phenyl-4-ethoxyethylidene-5(4*H*)-oxazolone isomers[23, 24].

Table 2. U.V. Spectral Data for Some Oxazolone Isomers and their Derivatives

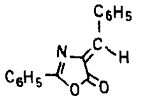
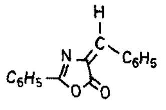
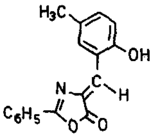
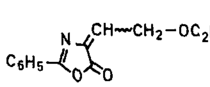
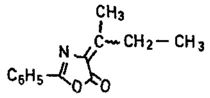
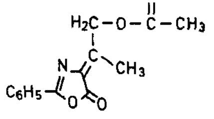
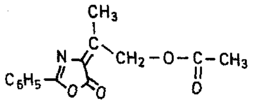
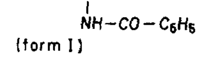
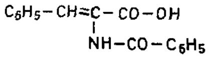
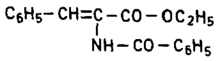
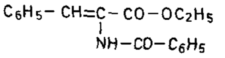
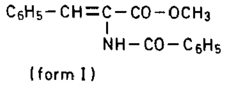
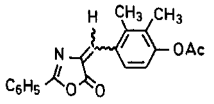
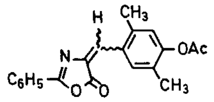
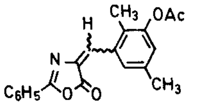
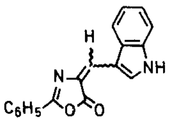
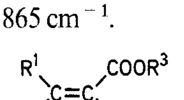
Compound	Solvent	λ ($\varepsilon_{max} \times 10^4$) nm	Reference
 **1**	C_2H_5OH	220 (0.97), 276 (—), 284 (1.31)	50, 51, 52
	C_2H_5OH	*259 (1.50), 360 (3.87)*	55
	95% C_2H_5OH	260 (2.1), 360 (5.5)	7
	95% C_2H_5OH	262 (—), 362 (5.37), 380 (3.92)	57
	$CHCl_3$	366 (3.9)	
	$CHCl_3$	262 (1.59), 365 (3.75)	51, 52
	$(C_2H_5)_2O$	360 (4.2)	56
	AcOH	259 (1.56), 361 (3.76)	54
	CH_3CN	226 (0.98), 234 (1.14), 239 (1.35), 247 (1.41), 259 (1.49), 328 (1.76), 347 (3.06), 361 (3.9), 380 (2.74)	9
	$(H_3C)_2CHOH$	*259 (2.65), 346 (3.2), 361 (4.2), 381 (—)*	36
	$(H_3C)_2CHOH$	259 (1.6), 344 (3.1), 360 (4.08), 380 (2.88)	38
 **2**	95% C_2H_5OH	260 (9), 360 (1.8)	7
	95% C_2H_5OH	262 (—), 362 (3.61), 380 (2.58)	57
	CH_3CN	*226 (0.96), 234 (1.02), 238 (1.11), 245 (1.02), 255 (0.69),* 328 (1.87), 350 (3.28), 361 (3.62), 380 (2.46)	9
	$(H_3C)_2CHOH$	224 (1.08), 238 (1.12), 243 (1.02), 362 (3.84)	38
	95% C_2H_5OH	*260 (—), 312 (0.72)*	40
	C_2H_5OH	325 (3.25), 340 (3.48)	21, 22
Isomer	C_2H_5OH	335 (3.2), 350 (2.8)	21, 22
	C_2H_5OH	290 (22), 310 (21)	23, 24
Isomer	C_2H_5OH	298 (7.8), 312 (8)	23, 24
 **7**	c-C_6H_{12}	225 (4.0), 230 (4.03), 236 (4.07), 244 (4.07), 306 (4.28), 323 (4.19)	11
 **8**	c-C_6H_{12}	232 (4.05), 237 (4.07), 245 (4.06), 306 (4.37), 323 (4.21)	11
 $C_6H_5-CH=\underset{NH-CO-C_6H_5}{C}-CO-OH$ (form I)	95% C_2H_5OH	222 (1.8), 279 (1.7)	54
	95% C_2H_5OH	*280 (1.4)*	7
	C_2H_5OH	222 (1.7), 280.5 (1.634)	57
	CH_3CN	278 (1.44)	9
 $C_6H_5-CH=\underset{NH-CO-C_6H_5}{C}-CO-OH$ (form II)	95% C_2H_5OH	*293 (1.778)*	57
	C_2H_5OH	300 (1.7)	7
	CH_3CN	302 (1.78)	9
 $C_6H_5-CH=\underset{NH-CO-C_6H_5}{C}-CO-OC_2H_5$ (form I)	95% C_2H_5OH	*222 (1.9), 282 (1.8)*	54
	95% C_2H_5OH	222 (1.95), 282 (1.8)	57
 $C_6H_5-CH=\underset{NH-CO-C_6H_5}{C}-CO-OC_2H_5$ (form II)	95% C_2H_5OH	225 (1.6), 292 (1.83)	57

Table 2. (continued)

Compound	Solvent	λ ($\varepsilon_{max} \times 10^4$) nm	Reference
 $C_6H_5{-}CH{=}C(NH{-}CO{-}C_6H_5){-}CO{-}OCH_3$ (form I)	CH_3CN	280 (2.2)	9
		*trans* 220 (4.0), 310 (3.77) *cis* 225 (3.85), 285 (3.75)	87 87
		*trans* 235 (4.35), 320 (4.08) *cis* 215 (4.28), 310 (4.05)	87 87
		*trans* 230 (3.88), 290 (3.5) *cis* 225 (3.80), 290 (3.68)	87 87
		280 (4.25), 425 (4.75) red and yellow isomers	99

5.1.2. I.R. Spectra

Studies of the infrared spectra of the geometric isomers have not been extensive. The I.R. spectra of compounds **1** and **2** showed[9] marked differences in the bands 1780 (s), 980 (m), and 870 (m) cm^{-1} for **1** and 1780 (m), 1010 (m), 900 (s), 795 cm^{-1} (doublet) for **2**. Compound **2**, prepared by photoisomerization, was reported[38, 90] to have bands at 1817, 1795, and 1772 cm^{-1} for carbonyl absorption. The absorption band at 1817 cm^{-1}, which is characteristic of saturated azlactones, seems out of place for **2**. However, the spectra of ethyl α-benzamidocinnamate isomers **24**, **25** do show differences[57]. Compound **24** shows bands at 1710, 1098, 1085, 1065, 890, 880, and 855 cm^{-1} doublet, whereas compound **25** has absorptions at 1700, 1080, 900, 875, and 860 cm^{-1}. Similarly, differences[8] do exist in the infrared spectra of the two isomers of α-benzamidocinnamic acid (**26** and **27**). Compound **27** absorbs at $\nu = 3400$, 1690, 1645, 1510, 1435, 1110, and 975 cm^{-1} while its (*Z*) isomer **26**, absorbs at $\nu = 3390$, 3200–3000 (broad band), 1720, 1635, 1550, 1540, 1100, 980, 965, and 865 cm^{-1}.



	R^1	R^2	R^3
24	C_6H_5	H	C_2H_5
25	H	C_6H_5	C_2H_5
26	C_6H_5	H	H
27	H	C_6H_5	H

5.1.3. N.M.R. Spectra

Nuclear magnetic resonance data for compounds **1** and **2** are available[38, 57, 58, 59]. Similar data have been reported for compounds **3** and **4** as also for the corresponding esters[10]. Based on the work on compounds **3** and **4**, the ethyl esters of the corresponding acids, and comparison with 3-benzamidocoumarin, substituent effects for the benzamido group have been calculated for the *cis* and *trans* isomers and values for methyl α-benzamidoacrylate are calculated and are in agreement with observed values. By comparing these data with the data for ethyl α-benzamido-3,4-dimethoxycinnamates, it has been proven that the higher melting isomer has the *trans* structure while the lower melting isomer has *cis* configuration, thus establishing the configurations of **3** and **4**. The N.M.R. spectra of oxazolones show the deshielding influence of the *cis*-$N{=}C{-}C_6H_5$ moiety on the olefinic hydrogen atom which shifts more downfield than when the olefinic hydrogen is *cis* to the carbonyl group. Sidhu and coworkers confirmed these observations[93].

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The N.M.R. spectra of ethyl α-benzamidocinnamate isomers have signals for the olefinic protons at $\delta = 7.6$ and 7.8 ppm showing that in the labile isomer the olefinic hydrogen atom is *cis* to the NH—CO—C_6H_5 group. N.M.R. data for 2-phenyl-4-(2-acetoxy-1-methylethylidene)-5(4*H*)-oxazolone have been reported[11]. Structural assignments for 2-phenyl-4-(3′,4′-dimethoxy-6′-alkyl)-benzylidene-5(4*H*)-oxazolones (where the 6′-alkyl groups are methyl, ethyl, isopropyl, and *t*-butyl) have been made on the basis of N.M.R. data. These compounds have all been assigned the (*Z*) configuration[10b, c]. Recently 2-(*cis*-2-butenyl)-4-benzylidene-5(4*H*)-oxazolone and 2-(*cis*-1-methylstyryl)-4-benzylidene-5(4*H*)-oxazolone have been prepared both by the Perkin-Erlenmeyer reaction as also by the double dehydrobromination reaction. Based on N.M.R. data, these compounds, have been assigned the (*Z*) configuration at the 4 position[83, 84].

Table 3. ¹H-N.M.R. Data for Some Oxazolone Isomers and their Derivatives

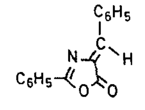
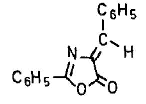
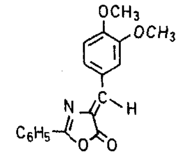
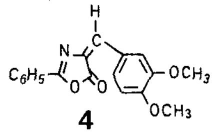
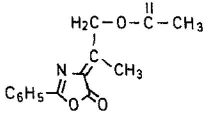
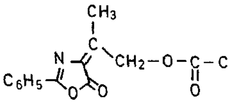
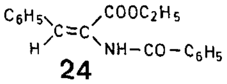
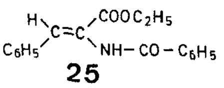
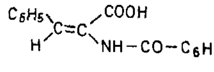
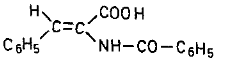
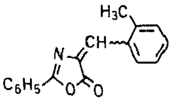
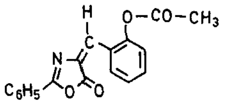
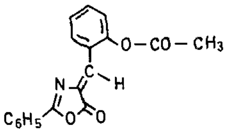
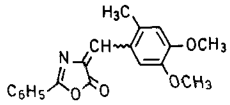
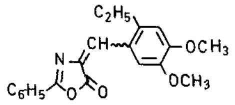
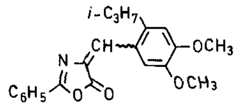
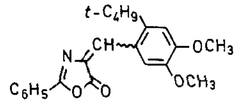
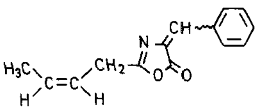
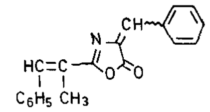
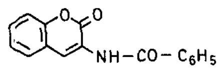
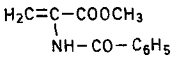
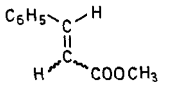
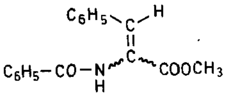
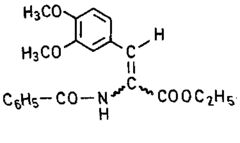
Compound	Solvent	δ (ppm)	Reference
 1	$CDCl_3$	7.21 (olefinic H)	38
	$CDCl_3$	7.21 (olefinic H), 7.35–7.7 (m, $6H_{arom}$), 8.1–8.4 ($4H_{arom}$, *o-positions*)	57
	$CDCl_3$	7.21 (olefinic H), 7.5 (m, $6H_{arom}$), 8.2 ($4H_{arom}$, *o*-positions)	59
	Ac_2O	7.27 (olefinic H)	58
 2	$CDCl_3$	7.5 (11H), 8.13 ($4H_{arom}$, *o*-positions)	38
	$CDCl_3$	7.2–7.6 (m, 7H), 7.9–8.4 (m, $4H_{arom}$, *o*-positions)	57
	Ac_2O	7.39–7.68 (olefinic H)	58
 3	$CDCl_3$	8.14 (H-2), 7.56 (H-6), 7.15 (olefinic H), 693 (H-5), 4.00, 3.94 (OCH_3)	10
 4	$CDCl_3$	8.36 ($3H_{arom}$), 7.52 (H-6), 7.48 (olefinic H), 6.90 (H-5), 3.99, 3.93 (OCH_3)	10
 7	$CDCl_3$	5.24 (=C(CH_3)—C$\underline{H}_2$—O), 2.4 (CH_3), 2.15 ($\underline{H}_3C$—CO—)	11
 8	$CDCl_3$	5.35 (=C(CH_3)—$\underline{C}H_2$—O), 2.33 (CH_3), 2.10 ($\underline{H}_3C$—CO—)	11
 24	$CDCl_3$	8.1 (s, 1H), 8.0–7.2 (m, 11H), 4.45–3.95 (q, CH_2), 1.2–0.9 (t, CH_3)	57 57
 25	$CDCl_3$	8.00–7.75 + 7.6–7.2 (2m, 12H), 4.5–4.15 (q, CH_2), 1.5–1.25 (t, CH_3)	57 57
 26	CD_3—SO—CD_3	9.8 (1H, acid H), 8.1–7.8 (m), 7.6–7.2 (m), 6.75 (s)	57
 27	CD_3—SO—CD_3	9.24 (1H, acid H), 8.1–7.95 + 7.75–7.25 (2m, 12H)	57
	$CDCl_3$	8.8 (1H), 8.2 (2H), 7.6–7.2 (*olefinic H* masked by H_{arom})	59

Table 3. (continued)

Compound	Solvent	δ (ppm)	Reference
 (E)	$CDCl_3$	8.6 (m, 6H), 7.64 (s, olefinic H)	39
 (Z)	$CDCl_3$	8.95 (m), 7.35 (s, olefinic H)	39
	$CDCl_3$	8.6 (H-2′), 6.71 (H-5′), 7.44 (=CH—), 4.01 + 3.90 (OCH_3), 2.31 (CH_3)	10c
	$CDCl_3$	8.64 (H-2′), 6.73 (H-5′), 7.47 (=CH—), 4.02 + 3.93 (OCH_3), 2.84 + 1.27 (C_2H_5)	10c
	$CDCl_3$	8.63 (H-2′), 6.85 (H-5′), 7.62 (=CH—), 4.02 + 3.94 (OCH_3), 3.50 + 1.29 (i-C_3H_7)	10c
	$CDCl_3$	8.55 (H-2′), 8.00 (=CH—), 7.02 (H-5′), 4.03 + 3.97 (OCH_3), 1.53 (t-C_4H_9)	83
	CCl_4	8.02, 7.32 ($5H_{arom}$), 6.96 (=C$\underline{H}$—C_6H_5), 6.83 (=CH—), 2.04 (CH_3)	83
	$CDCl_3$	8.02, 7.38 ($10H_{arom}$), 7.55 (C_6H_5—C$\underline{H}$=C<), 7.04 (=C$\underline{H}$—), 2.3 (CH_3)	83
	$CDCl_3$	9.0 8.7 (N$\underline{H}$), 8.83 (H-4)	10
$H_2C{=}CH{-}COOCH_3$	$CDCl_3$	6.38 (H_A), 5.82 (H_B)	10
 $H_2C{=}C(NH{-}CO{-}C_6H_5){-}COOCH_3$	$CDCl_3$	680 (H_A), 6.01 (H_B)	10
	$CDCl_3$ $CDCl_3$	(*cis*) 6.91 (olefinic H) (*trans*) 7.71 (olefinic H)	58 58
	$CDCl_3$ $CDCl_3$	(stable) 7.28 7.65 (olefinic H) (labile) 7.71 8.00 (olefinic H)'	58 58
	$CDCl_3$ $CDCl_3$	(stable) 7.7 8.1 (NH), 7.44 (olefinic H) 7.11 (H-2), 7.10 (H-6), 6.79 (H-5), 3.82, 3.64 (labile) 8.37 (NH), 8.00 (olefinic H), 6.90 (H-2, H-5, H-6)	10 10

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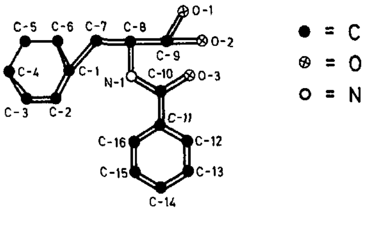
5.1.4. X-Ray Data

X-ray analysis of α-benzamidocinnamic acid (**27**) has shown it to have the *trans* configuration[49].

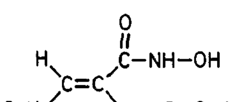


α-benzamido-trans-cinnamic acid—configuration viewed from the a-axis.

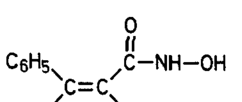
However, comparative X-ray crystallographic data for compounds **1** and **2** are not available.

5.1.5. pK_a Determinations

The pK_a values for *trans*-α-benzamidocinnamoylhydroxamic acid (**28**) and its *cis* isomer **29** have been determined[8] by potentiometric titrations.



28 pk_1 = 7.9 (–NH–OH)
pk_2 = 8.4 (–NH–CO–C_6H_5)

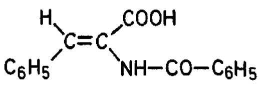


29 pk_1 = 7.6 (–NH–OH)
pk_2 = 8.7 (–NH–CO–C_6H_5)

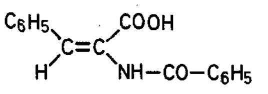
The acidity constant K_1 will be greater for **28** than for **29** since both the phenyl and hydroxamic acid groups are *trans* to each other. The value of K_2 will be greater for **29** than for **28** since in **29** the phenyl and benzamido groups are *trans-trans* to each other. The pK_a values for *trans*-α-benzamidocinnamic acid (**27**) and *cis*-α-benzamidocinnamic acid (**26**) were measured spectrophotometrically[46].

$$pk_a = pH + \log\left(\frac{d - d_i}{d_m - d}\right)$$

d_i = optical density of ion (basic solution)
d_m = optical density of molecule (acidic solution)
d = optical density of ion and molecule (at experimental pH)



27 pk_a = 3.53



26 pk_a = 2.78

Based on the arguments given above, it appears that the acid **27** has the *trans* configuration, while the acid **26** has the *cis* configuration.

5.1.6. Thermal Conversion

It has been observed that 2-phenyl-4-benzylidene-5(4*H*)-oxazolone (**2**) is converted quantitatively by heating at its melting point to **1**[36, 38]. Based on this observation, **2** has been assumed to have the *syn* configuration.

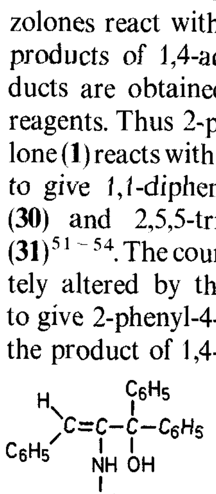
In a similar way, the structure of the geometric isomers of **10** may be assumed to be **10a** for the 95–96° melting isomer and **10b** for the 144–145° melting isomer since **10b** isomerizes to **10a** at 100° and as such has the *syn* configuration[16]. However, Brown and Smale[82] have shown that the lower melting isomer has *cis* configuration.

5.2. Chemical Properties

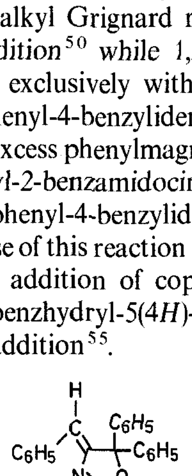
It should be pointed out that acid or basic hydrolyses and alcoholyses of oxazolones are always assumed to give isomeric acids and esters, with retention of configuration. Reactions towards other reagents such as Grignards and so on will be discussed.

5.2.1. Reaction towards Grignard Reagents

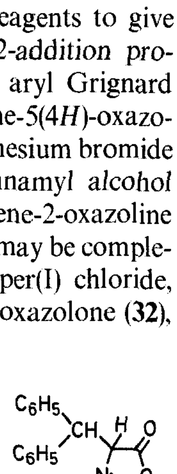
Earlier work has shown that 4-arylidene-5(4*H*)-oxazolones react with alkyl Grignard reagents to give products of 1,4-addition[50] while 1,2-addition products are obtained exclusively with aryl Grignard reagents. Thus 2-phenyl-4-benzylidene-5(4*H*)-oxazolone (**1**) reacts with excess phenylmagnesium bromide to give 1,1-diphenyl-2-benzamidocinnamyl alcohol (**30**) and 2,5,5-triphenyl-4-benzylidene-2-oxazoline (**31**)[51–54]. The course of this reaction may be completely altered by the addition of copper(I) chloride, to give 2-phenyl-4-benzhydryl-5(4*H*)-oxazolone (**32**), the product of 1,4-addition[55].



30



31



32

Under similar conditions, compound **2** reacts with phenylmagnesium bromide to give a 40% yield of **32**. Lesser amounts of **30** (20%) and **31** 10% and an uncrystallizable oil were also isolated[28, 31]. The formation of **30** and **31** from **2** strongly suggests the isomerization of **2** to **1** followed by ring opening since 1,2-addition to **2** would have given compounds isomeric with **30** and **31**. Other aryl Grignard reagents react with **2** to give analogs of **32** along with 1,2-addition products similar to **30** (see Table 4). In the presence of copper(I) chloride, phenylmagnesium bromide reacts with **2** to give **32** exclusively[24].

Reaction of 2-phenyl-4-benzylidene-5(4*H*)-oxazolone (2) with Phenylmagnesium Bromide:

To an ether solution of phenylmagnesium bromide [0.0375 mol prepared from magnesium (0.9 g), bromobenzene (5.9 g), and ether

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[64] R. Filler, J. D. Wismar, *J. Org. Chem.* **22**, 853 (1957).

[65] W. I. Awad, M. S. Hafez, *J. Org. Chem.* **25**, 1180, 1183 (1960).

[66] R. Filler, Y. S. Rao, *J. Org. Chem.* **27**, 3348 (1962).

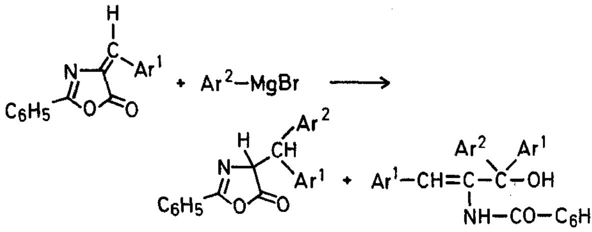
[67] R. Filler, K. B. Rao, unpublished results.

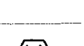
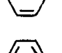
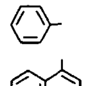
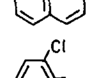
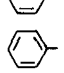
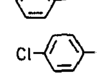
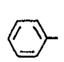
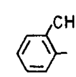
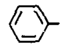
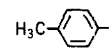
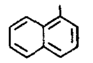
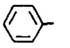
[68] H. Behringer, H. W. Stein, *Chem. Ber.* **82**, 209 (1949).

[69] H. Behringer, J. W. Jepson, *Chem. Ber.* **85**, 138 (1952).

(25 ml)] was added compound **2** (3.1 g; 0.0125 mol) suspended in 125 ml of dry ether during 1 h. The mixture was heated under reflux for 2 h and decomposed with saturated ammonium chloride solution. The ether layer was washed and dried over anhydrous magnesium sulfate. Ether was removed by flash evaporation, the oily residue was triturated with absolute ethanol and left overnight in a refrigerator. Compound **32**, m.p. 159°, which separated out, was filtered and recrystallized from ethanol; yield: 1.62 g (40%). The filtrate was concentrated, dissolved in ether, and treated with petroleum ether to give **30**; yield: 1.1 g; m.p. 164°. The residue after the removal of **30** was eluted over alumina to give **31**; yield: 0.5 g; m.p. 142°.

Table 4. Reaction of Geometric Isomers of 5(4*H*)-Oxazolones with Aryl Grignard Reagents[30]

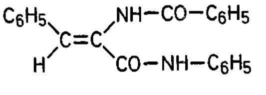


Ar¹	Ar²	Yield (%) of 1,4 product	M.p.	Yield (%) of 1,2 product	M.p.
		40	159°	20[a]	164°
		35	205°	45	166°
		39	175°	30	187°
		41	149°	25	191°
		30	113°	40	174°
		25	145°	35	185°
		30	205°	32	117°

[a] Compound **31** was obtained in 10% yield possibly formed by the dehydroactive cyclization of **30** on alumina[67].

5.2.2. Reactions with Amines

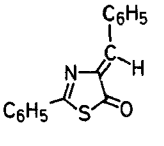
It has been pointed out earlier that the labile geometric isomers of oxazolones are converted to the stable isomers in the presence of pyridine and other tertiary amines. In the presence of aniline hydrochloride, both compounds **1** and **2** gave the same anilide, **33**, with aniline. Evidently **2** must have isomerized to **1** in the presence of aniline[24].



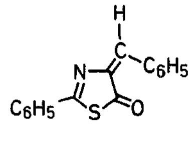
33

5.2.3. Reaction with Thioacids

Oxazolones react with thioacids such as thiolacetic acid to give thiazolones[68, 69, 70]. Thus, compound **1** gave 2-phenyl-4-benzylidene-5(4*H*)-thiazolone (**34**) on reaction with thiolacetic acid in the presence of triethylamine.



34

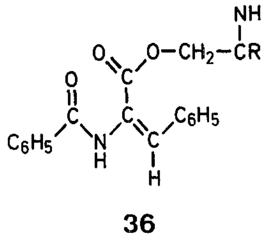


35

Compound **2**, on the other hand, gave on reaction with thiolacetic acid compound **35**, the geometric isomer of **34**[71]. It is interesting to note that **35** is the higher melting isomer (139°) while **34** obtained from **1** is the lower melting isomer (m.p. 131°).

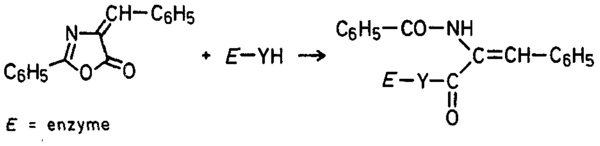
5.2.4. Reactions with Enzymes

The reaction of α-chymotrypsin with compound **1** has been extensively studied[9, 72–76]. When **1** reacts with α-chymotrypsin[72, 73, 74], the oxazolone disappears rapidly with the formation of two new species, depending on pH. At pH = 5, a species with a maximum at 305 nm, postulated to be an acyl enzyme involving a histidine residue was formed, while at pH = 8 (λ_{max} = 285 nm), a species of acyl enzyme involving a serine moiety was postulated. The identity of the second species was questioned and it was shown to be **36**[75, 76].



36

The reaction of either isomer **1** or **2** could lead to the formation of an acyl-enzyme as shown below.



E = enzyme
Y = active site

37

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[70] S. I. Lure, L. G. Gatsenko, *J. Gen. Chem. USSR* **22**, 321 (1952).

[71] R. Filler, Y. S. Rao, *J. Org. Chem.* **27**, 3730 (1962).

[72] K. Brocklehurst, K. Williamson, *J. Chem. Soc. Chem. Commun.* **1966**, 462.

[73] K. Brocklehurst, K. Williamson, *J. Chem. Soc. Chem. Commun.* **1967**, 666.

[74] K. Brocklehurst, K. Williamson, *Biochem. Biophys. Res. Commun.* **26**, 175 (1967).

[75] J. de Jersey, B. Zerner, *Biochem. Biophys. Res. Commun.* **28**, 173 (1967).

[76] J. de Jersey, B. Zerner, *Biochemistry* **8**, 1975 (1969).

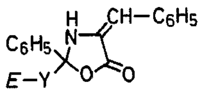
[77] E. Baltazzi, R. Robinson, *Chem. Ind. (London)* **1953**, 541

[78] N. K. Kochetkov, E. I. Budovskii, R. M. Khomutov, M Y. Karpeiskii, *J. Gen. Chem. USSR* **29**, 70 (1959).

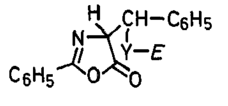
[79] K. R. Hanson, R. H. Wightman, J. Staunton, A. R. Battersby *J. Chem. Soc. Chem. Commun.* **1971**, 185.

[80] R. H. Wightman, J. Staunton, A. R. Battersby, *J. Chem Soc. Perkin. Trans. I* **1972**, 2355.

The products are likely to be α-benzamidocinnamoyl- α-chymotrypsins, **37**. Other structures such as **38**, **39** cannot however be ruled out.



38

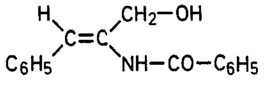


39

It was also observed that α-benzamido-*trans*-cinnamoyl-α-chymotrypsin (from **1**) gets hydrolyzed faster than α-benzamido-*cis*-cinnamoyl-α-chymotrypsin *(from* **2**) *in the pH range of 7–10.*

5.2.5. Reaction with Lithium Aluminium Hydride

Compound **1** reacts with lithium aluminium hydride to give α-benzamidocinnamyl alcohol **40**, (m.p. 127°) characterized as the *p*-nitrobenzoate ester[77]. Under similar conditions, compound **2** gave an oil, which did not crystallize out. *However this oil gave a p-* nitrobenzoate ester, identical with the one from **40**. Evidently isomerization of **2** to **1** must have occurred either during the lithium aluminium hydride reduction or during esterification[28].



40

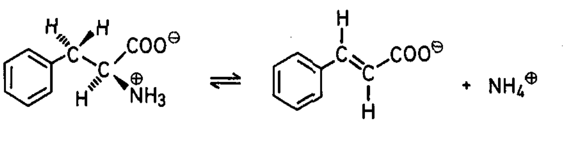
Reduction of 2-Phenyl-4-benzylidene-5(4*H*)-oxazolone 2 with Lithium Aluminium Hydride:
In a 3-necked, 250 ml round bottomed flask provided with a condenser, dropping funnel, thermometer, and magnetic stirrer was placed lithium aluminium hydride (3 g, 0.09 mol) in anhydrous ether (75 ml). The flask was cooled to −70° in an acetone/dry *ice bath. Compound* **2** *(1 g) in ether (25 ml) was added during* a 0.5 h period. The temperature was kept below −30°. The mixture was stirred for an additional 3 h period. Ethyl acetate (20 ml) was added followed by a saturated solution of ammonium chloride. The organic layer was separated, treated with absolute ethanol (25 ml), and filtered. The filtrate, on concentration, gave an oil, which did not crystallize; yield: 0.6 g (60%) The *p*-nitrobenzoate ester was prepared; m.p. 164° (Lit.[77] m.p. 165°).

5.2.6. *Reaction with Hydroxylamine Acetate*

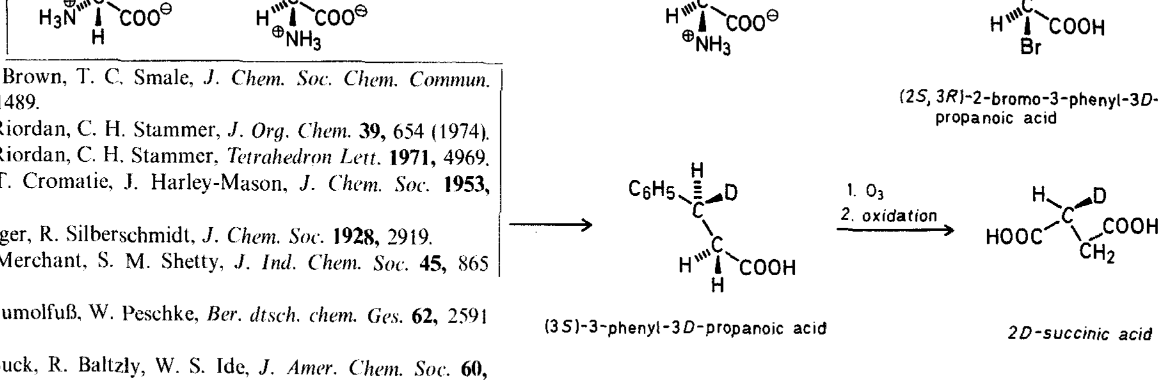
Compounds **1** and **2** react with hydroxylamine acetate at room temperature to give **28** and **29**[8, 78].

6. Structure Proof by Degradation

A recent study of the enzyme[79, 80, 81] catalyzed elimination of a proton and ammonia from L-phenylalanine to give *trans*-cinnamate ion supports the *trans*-configuration "(*Z*)" for **1**. (Some confusion seems to exist about the *cis,trans* nomenclature for 2-phenyl-4-benzylidene-5(4*H*)-oxazolone. Thus, Niemann and coworkers called **1** the *cis*-oxazolone since the exocyclic phenyl group and the N-atom are *cis* to each other, while *cis* 2-phenyl-4-benzylidene-5(4*H*)-oxazolone, according to Zerner, et al. and Brocklehurst and Williamson, refers to the oxazolone in which the exocyclic phenyl group and the carbonyl group are *cis* to each other (i.e. compound **2**). Battersby and coworkers use the (*Z*, *E*) designations. Thus, compound **1** has the (*Z*) configuration while **2** may be designated (*E*).)



The configuration at C-3 of the L-phenylalanine was established by a series of conversions, summarized below in Scheme A.



Scheme A

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[81] P. G. Strange, J. Staunton, H. R. Wiltshire, A. R. Battersby, K. R. Hanson, E. A. Havir, *J. Chem. Soc. Perkin Trans. I* **1972**, 2634.

[82] A. G. Brown, T. C. Smale, *J. Chem. Soc. Chem. Commun.* **1969**, 1489.

[83] J. M. Riordan, C. H. Stammer, *J. Org. Chem.* **39**, 654 (1974).

[84] J. M. Riordan, C. H. Stammer, *Tetrahedron Lett.* **1971**, 4969.

[85] R. I. T. Cromatie, J. Harley-Mason, *J. Chem. Soc.* **1953**, 3525.

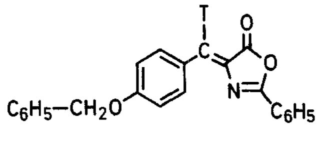
[86] G. Berger, R. Silberschmidt, *J. Chem. Soc.* **1928**, 2919.

[87] J. R. Merchant, S. M. Shetty, *J. Ind. Chem. Soc.* **45**, 865 (1968).

[88] H. Schumolfuß, W. Peschke, *Ber. dtsch. chem. Ges.* **62**, 2591 (1929).

[89] J. S. Buck, R. Baltzly, W. S. Ide, *J. Amer. Chem. Soc.* **60**, 1789 (1938).

If *syn* addition of hydrogen is accepted in step (3), then compound **41** has to have the (*Z*) configuration. Similar structural assignment has been made for the azlactone from 4-benzyloxy-[formyl-^{3}H]-benzaldehyde (**42**).



42

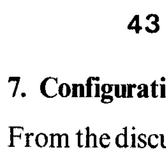
Yet another degradation reaction studied was the decarboxylation of α-benzamidocinnamic acid isomers in diglyme/copper chromite. Only one product, β-benzamidostyrene[57], (m.p. 186°) was obtained.

$C_6H_5{-}CH{=}CH{-}NH{-}CO{-}C_6H_5$

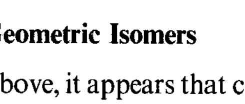
43

7. Configuration of Geometric Isomers

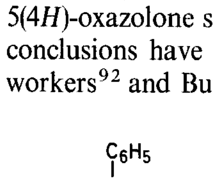
From the discussion above, it appears that configurations of the geometric isomers of 2-phenyl-4-benzylidene-5(4*H*)-oxazolone and 2-phenyl-4-veratrylidene-5(4*H*)-oxazolone seem to have been settled. Similar conclusions have been reported by White and coworkers[92] and Burger and coworkers[97, 98].



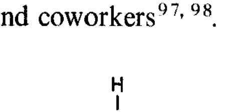
1 (*Z*)



2 (*E*)



3 (*Z*)



4 (*E*)

8. Note added in Proof

Geometric isomers of pseudoxazolones[102] and of oxazolones derived from penicillin[103, 104, 105] have been described. Warnhoff and coworkers[106] report the formation of a mixture of isomers from phenylacetone and hippuric acid. Based on their studies of N.M.R., U.V., and I.R. spectra, Bernabe and coworkers[107] conclude that oxazolones prepared by Perkin-Erlenmeyer reaction have the *trans* or (*Z*) configuration. Siemion and coworkers[108] recently studied the O.R.D. and N.M.R. spectra of saturated oxazolones and reported that a folded conformation in which the aromatic ring faces the oxazolone ring is favored.

The reactions of **1** and **2** with enamines from cyclohexanone and morpholine give different products[109].

Finally a new and simple method of conversion of the stable isomers to labile isomers has been reported[110]. This method consists of heating the stable isomers with polyphosphoric acid at 85–90° for 90 minutes and the labile isomers are obtained exclusively. Polyphosphoric acid may also be used as a medium for the condensation of aromatic aldehydes with hippuric acid to give labile isomers[99, 111]. This method gives isomers from anisaldehyde for which isomers were predicted but never isolated[112].

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