

parison of the retention times with an authentic *cis-trans*-1,3,5-hexatriene mixture² indicated that the second and third peaks emanating from the chromatograph corresponded to *trans*- and *cis*-1,3,5-hexatrienes, respectively. Equilibration of the crude product with iodine resulted in the almost total conversion of the area of the third peak to that of the second, while reaction with maleic anhydride resulted in the removal of the second peak altogether, thus establishing the identity of the second and

third peaks as *trans*- and *cis*-1,3,5-hexatrienes, respectively. The peak attributable to *cis*-1,3,5-hexatriene represented approximately 60% of the total area and 85% of the trienic component.

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Studies on the Azidolysis of 4-Arylidene- and 4-Alkylidene-5-oxazolones

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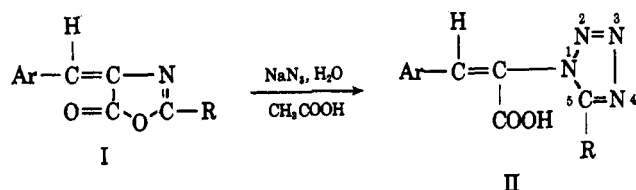
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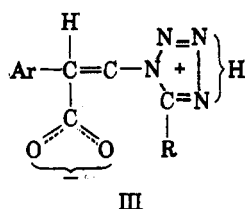
Tetrazolylcinnamic acid derivatives are prepared by a simple method in good yields. Infrared spectra of these acids revealed two types of acids in the solid state: (a) a dipolar type in equilibrium with its monomer, and (b) normal bonded acids. The ultraviolet spectra show that the methyl group in the 5-position has no interaction with the tetrazolyl ring while a phenyl group has. Under similar conditions 4-isopropylidene- and 4-cyclohexylidene-5-oxazolones gave no tetrazolylacrylic acid derivatives and the reaction proceeds *via* another route with decarbonylation to give Va, Vb, and VII. The constitution of these products is discussed in the light of their ultraviolet, infrared, and n.m.r. spectra.

Behringer and Grimure² found that 4-arylidene-5-oxazolones react with hydrazoic acid in chloroform in a sealed tube or with a mixture of sodium azide and aluminum chloride in tetrahydrofuran to give α -(1-tetrazolyl)acrylic acid derivatives (II).

In the present investigation a simpler method, giving much better yields (*cf.* Table II), for the preparation of α -(1-tetrazolyl)acrylic acid derivatives has been found, and some new acids have been synthesized according to the following scheme. The structure of these products



is established by a study of their infrared and ultraviolet spectra. Thus, the infrared spectra revealed two types of acids: (a) normal acids which show a bonded OH stretching frequency in the region 2700–2500 cm^{-1} (weak)^{3a} (these acids are IIa, c, and g-o); and (b) acids which exist in zwitterionic form (*cf.* III) in equilibrium with the nonpolar monomer form (IIb and d-f) since their infrared spectra show three main bands in the ranges 3500–3450 cm^{-1} for acidic OH,^{3a} 2500–2440 and 1900–1886 cm^{-1} for $+\text{NH}$,^{3b} and about 1700 cm^{-1} for $\text{C}=\text{O}$.^{3a} The acids that show dipolar character are those having an electron-attracting



group in the aromatic moiety of the cinnamyl part of the molecule.

Methylation of IIa (diazomethane) gave the corresponding ester, and its infrared spectrum revealed a shift in the $\text{C}=\text{O}$ stretching frequency to 1730 cm^{-1} .

The bands in the region 985–1110 cm^{-1} appear to be characteristic of the tetrazole ring modes.⁴

The ultraviolet spectra of some 1,5-disubstituted tetrazoles were investigated by Roberts, Fanta, and Martin.⁵ Cinnamic acid^{6a} showed λ_{max} 273 $\text{m}\mu$ (ϵ_{max} 20,000). Most of the acids under investigation (*cf.* Table II) show more than one maximum. The maxima at shorter wave lengths can be attributed to the tetrazolyl moiety and those at longer wave lengths can be attributed to the cinnamyl moiety.

Elpern and Nachod⁷ showed that the tetrazolyl ring had little or no absorption in the usual ultraviolet region. In the compounds under investigation (*cf.* Table II), if we compare the ultraviolet spectrum of IIa with that of IIk or the spectrum of IIb with that of III where the methyl group replaces a phenyl group in the 5-position, it is only the absorption due to cinnamyl moiety that appears. This favors the conclusion reached by Roberts, *et al.*,⁵ and Garbrecht and Herbst.⁸

The values for IIh and IIn are rather similar, and are comparable with those of *p*-methoxycinnamic acid, λ_{max} 224 $\text{m}\mu$ (ϵ_{max} 22,000) and 289 $\text{m}\mu$ (ϵ_{max} 28,000). The values for IIj and IIo can be attributed to the 3,4-methylenedioxycinnamic acid moiety as the values for 3,4-methylenedioxycinnamic acid are: λ_{max} 225 $\text{m}\mu$ (ϵ_{max} 28,900), 283 (26,830), and 313 (26,300). IIf showed only one band, which is actually a broad one and might have masked the band due to the tetrazolyl moiety. The ultraviolet spectra are thus not helpful in distinguishing acids that show dipolar character.⁹

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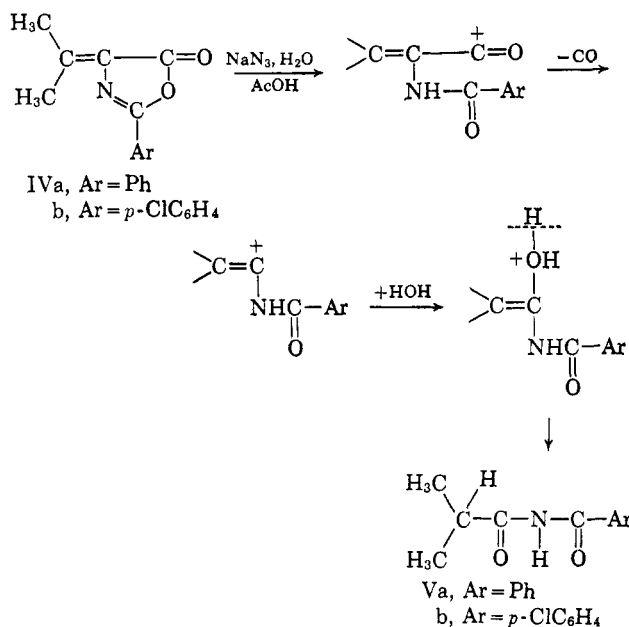
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The formation of the tetrazoles II by cleavage at the 2-carbon of I is contrary to the normal oxazolone ring opening.^{10,11} Upon extending the same reaction to 2-aryl-4-isopropylidene-5-oxazolone (IV) and 2-phenyl-4-cyclohexylidene-5-oxazolone, a neutral compound was obtained as the main product, indicating that the reaction proceeds *via* another course. Analysis of these products revealed that the azido group was not incorporated in the products, and that one carbon atom was lost. The infrared spectra of these compounds (*cf.*

TABLE I

Compd.	λ_{\max} , m μ (ϵ_{\max})	ν_{NH} , cm. ⁻¹	$\nu_{\text{C=O}}$, cm. ⁻¹	
			Conjugated with aromatic moiety	
Va	234 (11,500)	3300	1724	1666
Vb	244 (15,800)	3333	1750	1695
VII	233 (13,400)	3333	1724	1690
	275 (1,700)			

Table I) revealed a strong NH stretching frequency and two carbonyl stretching frequencies. The following mechanism is thus proposed.

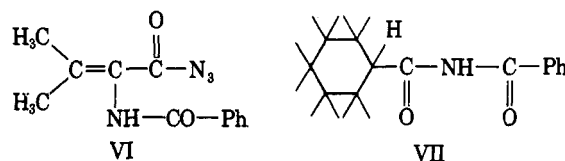


The n.m.r. spectrum of Va confirms this structure. It showed peaks at τ = 8.69 (6H) and 6.3 (m, 1H) for an isopropyl group, 1.97–2.15 and 2.30–2.54 (3- and 2-protons) for the phenyl group, and 1.06 p.p.m. for CO—NH—CO. Va has been finally synthesized from isobutyryl chloride and benzamide and proved to be identical by mixture melting point determination. The melting point of Va was stated in the literature as 121°,¹² and later as 155°^{13a} and 154–155°.^{13b} The

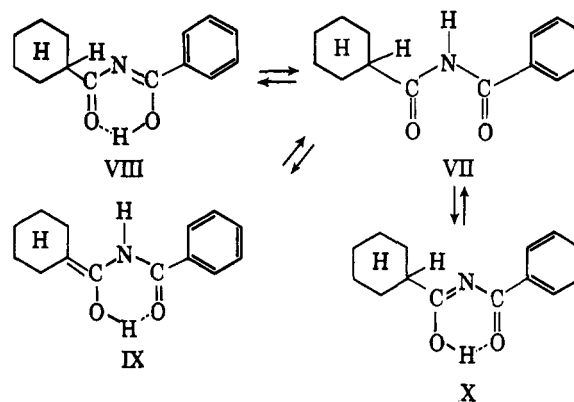
decarbonylation that occurred in such a reaction is known in similar structures.¹⁴ Water is essential in this reaction. Upon carrying out this reaction in anhydrous tetrahydrofuran in the presence of anhydrous aluminum chloride, only α -benzamido- β , β' -dimethylacrylic acid was obtained.

A mechanism for the formation of Va from IVa involving formation of the azide VI can be excluded, since this azide is known¹⁵ to decompose giving rise to the corresponding oxazolone (IVa). We have also heated VI under the same experimental conditions of the formation of Va and obtained only the oxazolone IVa.

2-Phenyl-4-cyclohexylidene-5-oxazolone gives VII by a similar mechanism. Its n.m.r. spectrum showed peaks at τ = 6.8–8.9 (cyclohexyl protons), 1.97–2.15 and 2.3–2.54 (3- and 2-protons) for the phenyl group,



and 1.06 p.p.m. for CO—NH—CO. The peak at τ = 6.3 p.p.m. is also attributed to the tertiary proton neighboring the carbonyl group. A new peak appears in the spectrum of this compound at τ = 3.6 p.p.m. The integral of the signals at τ = 1.06, 3.6, and 6.6 p.p.m. is approximately equal to two protons and the band at τ = 3.6 p.p.m. can be attributed to the proton of an enol form (*cf.* VIII, IX, and X).



The ultraviolet spectra of Va, Vb, and VII show that they are of similar constitution (*cf.* Table I). The ultraviolet spectrum of VII shows, besides the band at λ_{\max} 233 m μ , a shoulder at λ 275 m μ (ϵ_{\max} 1700) which can be attributed to the enol form^{6b} (*inter alia*). In the case of Vb and VII a small fraction of acidic by-products was obtained. The analysis of each does not fit with the corresponding tetrazolylacrylic acid derivative and its constitution is still under investigation.

Experimental

Melting points are not corrected. Analyses were carried out by Alfred Bernhardt, Max Planck Institute, Mülheim, Germany. Infrared spectra were measured on a Perkin-Elmer Infracord Model 137 spectrophotometer using KBr wafer technique.

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Ultraviolet spectra were measured on a Perkin-Elmer Spectracord Model 4000A spectrophotometer using ethyl alcohol solutions. N.m.r. spectra were carried out using a 60-Mc. Perkin-Elmer spectrometer with CDCl_3 solutions.

Action of Hydrazoic Acid on 4-Arylidene-5-oxazolones (II).
General Procedure.—A solution of sodium azide (1 g. in the least amount of water) was added to a solution of I (1 g. in the least amount of glacial acetic acid) and the mixture was heated on a water bath for 1–6 hr. It was then poured on crushed ice and the precipitate was collected and dissolved in NaHCO_3 solution. The latter was ether extracted and the aqueous layer was then acidified with cold dilute hydrochloric acid. The precipitated acid was collected, washed with cold water, and recrystallized from a suitable solvent (*cf.* Table II).

Action of Diazomethane on IIa.—A solution of IIa (2 g.) in ether (250 ml.) was treated with diazomethane solution (from 10 g. of nitrosomethylurea in about 250 ml. of ether) and left overnight in an ice chest. The solution was dried over anhydrous sodium sulfate and filtered and the solvent was distilled off. The oily residue was triturated with a little petroleum ether (b.p. 60–80°) and allowed to cool. The yellow substance which separated was collected and crystallized from methyl alcohol as pale yellow crystals, m.p. 130–132°, yield 47.8%.

Anal. Calcd. for $\text{C}_{17}\text{H}_{14}\text{N}_4\text{O}_2$: C, 66.66; H, 4.57; N, 18.30. Found: C, 66.67; H, 4.74; N, 18.34.

Effect of Heat on IIa.—IIa (1 g.) was heated at its melting point under vacuum for 0.5 hr. or until gas evolution stopped. The yellow product obtained was crystallized from ethyl acetate–petroleum ether to give 2-phenyl-4-benzal-5-oxazolone, m.p. and m.m.p. 164°.

Action of Hydrazoic Acid on 2-Phenyl-4-isopropylideneoxazolone (IVa).—A solution of sodium azide (1 g. in the least amount of water) was added to a solution of 2-phenyl-4-isopropylideneoxazolone solution (1 g. in the least amount of glacial acetic acid). The reaction mixture was heated on a boiling-water bath for 0.5 hr. It was poured on crushed ice and the solid product was filtered off. The product (Va) was crystallized from absolute ethyl alcohol in colorless needles, m.p. 154°, and shown to be N-isobutyrylbenzamide by mixture melting point, yield 83%.

Anal. Calcd. for $\text{C}_{11}\text{H}_{13}\text{NO}_2$: C, 69.09; H, 6.83; N, 7.33. Found: C, 69.05; H, 7.03; N, 7.39.

Preparation of N-Isobutyrylbenzamide (Va).—Isobutyryl chloride (10 g.) was added dropwise to a cold (*ca.* 10°) solution of benzamide (11 g.) in pyridine (60 ml.) and the temperature was maintained at about 10–15° during the addition. The reaction mixture was left at room temperature for 0.5 hr. It was poured on crushed ice and the precipitate was filtered off. This precipitate was digested in cold ether and filtered from the insoluble unchanged benzamide. Ether was then evaporated to give colorless crystals which were recrystallized from absolute ethyl alcohol as colorless needles (12 g.), yield 70%, m.p. 154°.

Action of Heat on α -Benzamido- β,β -dimethylacrylic Acid Azide (VI).¹⁵—A solution of VI (2 g. in 10 ml. of hot glacial acetic acid and 4 ml. of water) was heated on a boiling-water bath for 1 hr. The product was cooled and poured on crushed ice whereby a yellow precipitate separated out (1.5 g.) which was shown to be 2-phenyl-4-isopropylidene-5-oxazolone¹⁶ by mixture melting point.

Preparation of 2-(4-Chlorophenyl)-4-isopropylidene-5-oxazolone (IVb).—A mixture of *p*-chlorohippuric acid (10 g.), dry acetone (180 ml.), acetic anhydride (17 ml.), and sodium bicarbonate (4.6 g.) was refluxed for 6 hr., left to cool at room temperature, and filtered. The filtrate was poured on crushed ice and diluted with cold water to 1.5 l. The precipitate was filtered off and crystallized from petroleum ether (b.p. 100–120°) as pale yellow needles, m.p. 170–172°, yield 81%.

Anal. Calcd. for $\text{C}_{12}\text{H}_{10}\text{ClNO}_2$: C, 61.10; H, 4.24; Cl, 15.07; N, 5.94. Found: C, 61.06; H, 4.35; Cl, 14.37; N, 5.77.

Action of Hydrazoic Acid on IVb.—A solution of sodium azide (1 g.) in water (4 ml.) was added to a solution of IVb (1 g. in 6 ml. of hot glacial acetic acid). The reaction mixture was heated on a water bath for 3 hr., poured on crushed ice, and filtered. The precipitate was digested in sodium bicarbonate solution and filtered off. The residue (nonacidic fraction, 0.8 g.) was crystallized from petroleum ether (b.p. 100–120°) as colorless needles, m.p. 132–134°.

TABLE II
 α -(1-TETRAZOLYL)ACRYLIC ACID DERIVATIVES

Compd.	Ar	R	Reac- tion time, hr.	Crystn. solvent ^a	Yield, %	M.p., °C.	Formula	% C		% H		% N		λ_{max} , m μ	$\epsilon_{\text{max}} \times 10^3$
								Calcd.	Found	Calcd.	Found	Calcd.	Found		
IIa	C_6H_5	C_6H_5	1	A	76	198–200	$\text{C}_{16}\text{H}_{12}\text{N}_4\text{O}_2$	65.75	65.43	4.14	3.78	19.17	18.40	247, 263	0.189, 0.192
IIb	<i>p</i> -ClC ₆ H ₄	C_6H_5	1	A	87	192	$\text{C}_{16}\text{H}_{11}\text{ClN}_4\text{O}_2$ ^b	58.80	58.93	3.36	3.97	17.10	16.42	218, 225, 273	0.22, 0.213, 0.238
IIc	<i>m</i> -ClC ₆ H ₄	C_6H_5	1	A	74	152	$\text{C}_{16}\text{H}_{11}\text{ClN}_4\text{O}_2$ ^c	58.80	59.27	3.36	3.37			242, 251, 258	0.173, 0.17, 0.166
IId	<i>o</i> -ClC ₆ H ₄	C_6H_5	1	A	69	159–160	$\text{C}_{16}\text{H}_{11}\text{ClN}_4\text{O}_2$ ^d	58.80	58.19	3.36	3.80	17.10	16.55	223, 240, 252	0.179, 0.152, 0.143
IIf	<i>p</i> -NO ₂ C ₆ H ₄	C_6H_5	1	A	68	195	$\text{C}_{16}\text{H}_{10}\text{N}_6\text{O}_4$	56.97	57.53	3.29	3.75	20.77	19.83	230, 238, 294	0.115, 0.097, 0.107
IIg	<i>m</i> -NO ₂ C ₆ H ₄	C_6H_5	1	A	79	164–165	$\text{C}_{16}\text{H}_{10}\text{N}_6\text{O}_4$	56.97	57.05	3.29	3.46	20.77	19.31	248	0.169
IIh	<i>p</i> -CH ₃ OC ₆ H ₄	C_6H_5	1	A	97	175–176	$\text{C}_{16}\text{H}_{12}\text{N}_4\text{O}_4$	63.35	63.32	4.48	4.62	17.38	17.50	236, 305	0.257, 0.025
IIi	<i>p</i> -CH ₃ OC ₆ H ₄	C_6H_5	3	A	95	185	$\text{C}_{17}\text{H}_{14}\text{N}_4\text{O}_3$	67.91	67.71	4.43	4.82	17.60	17.03	225, 298	0.197, 0.202
IIj	$\text{C}_6\text{H}_5\text{CH}=\text{CH}$	C_6H_5	1	B	82	225	$\text{C}_{18}\text{H}_{14}\text{N}_4\text{O}_2$	60.71	60.34	3.60	3.93	16.66	16.77	232, 312	0.114, 0.131
IIk	$\text{CH}_3\text{O}_2\text{C}_6\text{H}_3$	CH_3	6	A	87	183	$\text{C}_{17}\text{H}_{12}\text{N}_4\text{O}_4$	57.38	57.64	4.38	4.33	24.38	24.05	235, 288, 321	0.182, 0.08, 0.12
IIl	C_6H_5	CH_3	1	B	70	204	$\text{C}_{11}\text{H}_{10}\text{N}_4\text{O}_2$	50.00	49.92	3.41	3.60	21.11	19.82	267	0.197
IIm	<i>p</i> -ClC ₆ H ₄	CH_3	1	B	91	190	$\text{C}_{17}\text{H}_9\text{ClN}_4\text{O}_2$ ^e	48.00	48.23	3.30	3.30	25.42	25.29	273	0.195
IIo	<i>m</i> -NO ₂ C ₆ H ₄	CH_3	1	A	80	193	$\text{C}_{17}\text{H}_9\text{N}_5\text{O}_4$	55.38	55.08	4.65	4.58	21.53	21.60	256	0.293
IIp	<i>p</i> -CH ₃ OC ₆ H ₄	CH_3	1	B	91	219	$\text{C}_{12}\text{H}_{12}\text{N}_4\text{O}_3$	59.50	59.19	4.16	4.51			222, 295	0.159, 0.244
IIq	$\text{CH}_3\text{O}_2\text{C}_6\text{H}_3$	CH_3	1	A	93	218	$\text{C}_{12}\text{H}_{10}\text{N}_4\text{O}_4$							235, 288, 323	0.305, 0.141, 0.198

^a A, ethyl acetate–petroleum ether (b.p. 60–80°); B, ethyl acetate. ^b *Anal.* Calcd.: Cl, 10.80. Found: Cl, 10.27. ^c *Anal.* Calcd.: Cl, 10.80. Found: Cl, 10.36. ^d *Anal.* Calcd.: Cl, 10.80. Found: Cl, 13.60. ^e *Anal.* Calcd.: Cl, 13.51.

Anal. Calcd. for $C_{11}H_{12}ClNO_2$: C, 58.5; H, 5.30; Cl, 15.70; N, 6.20. Found: C, 58.41; H, 5.57; Cl, 15.82; N, 6.05.

The filtrate was acidified with cold dilute HCl whereby a colorless product separated out, was filtered off, and crystallized from petroleum ether (b.p. 100–120°) as colorless needles, m.p. 210°.

Action of Hydrazoic Acid on 2-Phenyl-4-cyclohexylidene-5-oxazolone.—The experiment was carried out as described above. The nonacidic fraction was crystallized from ethyl acetate, m.p. 157°, yield 73%.

Anal. Calcd. for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.26; H, 7.56; N, 6.32.

The acidic fraction was crystallized from ethyl acetate as colorless needles, m.p. 204–208°.

Action of Sodium Azide and Aluminum Chloride in Tetrahydrofuran on IVa.—A solution of aluminum chloride (12 g.) in anhydrous tetrahydrofuran (250 ml.) was added dropwise to a well-stirred solution of IVa (18 g.) in anhydrous tetrahydrofuran containing sodium azide (29 g.). The reaction mixture was stirred for 10 hr. on a water bath. The complex was decomposed with 125 ml. of 6 N HCl while stirring for 1 hr. The tetrahydrofuran layer was separated and dried over anhydrous sodium sulfate. Tetrahydrofuran was removed to give a solid product

which was dissolved in ethyl acetate and, on addition of petroleum ether (b.p. 40–60°), a colorless material separated out which was filtered off and crystallized from ethyl acetate–petroleum ether (b.p. 40–60°) as colorless crystals (15 g.), m.p. 217°, shown to be α -benzamido- β,β' -dimethylacrylic acid by mixture melting point.

Action of Trichloroacetic Acid on IVa.—The experiment was carried out as described in the action of hydrazoic acid on IVa except that trichloroacetic acid was used instead of sodium azide. The product (1 g.) was crystallized from ethyl acetate–petroleum ether (b.p. 60–80°) and proved to be α -benzamido- β,β' -dimethylacrylic acid¹⁶ by mixture melting point.

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2-Amino-5-aryl-2-oxazoles. Tautomerism, Stereochemistry, and an Unusual Reaction

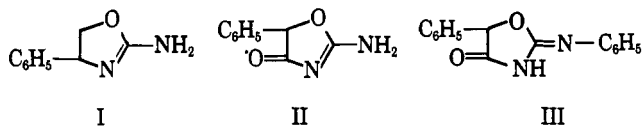
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The double bond of the 2-amino-5-aryl-4-methyl-2-oxazoles has been shown by infrared and proton magnetic resonance spectra to be endocyclic, regardless of the substituent on the amino group. Determination of stereochemistry in this series by n.m.r. spectra is discussed. 3,4-Dimethyl-2-methylimino-5-phenyloxazolidine (VIIa) reacts with phenyl isothiocyanate to give 3,4-dimethyl-5-phenyl-2-phenylimino-2-oxazolidine (VIIb).

2-Amino-4-phenyl-2-oxazoline (I) has been reported¹ to exist as the amino tautomer on the basis of infrared spectra and dissociation constant. This is consistent with the generalization² that amino tautomers are almost always more stable than their corresponding imino tautomers. However, ultraviolet spectral studies of the 2-amino-5-aryl-2-oxazolin-4-ones have indicated that, while the unsubstituted 2-amino compound (II) exists as the amino tautomer,³ the compound (III) bearing a phenyl group on the exocyclic nitrogen exists as the imino tautomer.^{3a}



In the course of our study of the appetite suppressant activity of the 2-amino-5-aryl-2-oxazoles,⁴ we have examined the spectra of a number of these compounds to gain insight into their tautomerism with particular reference to the effect of a substituent on the amino group.

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Discussion and Results

Tautomerism.—The infrared spectral evidence cited¹ by Pitha, Jonás, Kovár, and Bláha for the existence of I in the amino form is the absorption at 2.84 and 2.92 μ assigned to the asymmetric and symmetric stretch of the unassociated amino group and the band at 6.21 μ assigned to the $-NH_2$ deformation absorption. Based on a study of model compounds, they felt that the N–H stretching bands of the alternative imino form would appear at higher wave lengths. They observed the apparently anomalous fact that the C=N stretching band of I appears at a wave length closer to that of the oxazoline locked in the imino form by a methyl group at the 3-position than to the C=N absorption of the compound locked in the amino form by two methyl groups on the amino nitrogen. They rationalized this fact on the grounds that the wave length should be highly dependent on the degree of substitution on nitrogen as is the carbonyl absorption of amides.

The infrared spectra of the 2-amino-4-methyl-5-phenyl-2-oxazoles closely resemble the reported spectra of the 2-amino-4-aryl-2-oxazoles (see Table I). Compound IV, in very dilute solution in deuteriochloroform, exhibits N–H stretching bands at 2.83 and 2.92 μ . In more concentrated solution in chloroform, IV shows a C=N stretching band at 5.90 μ and a band, presumably due to NH_2 deformation, at 6.27 μ . Since the alternative imino form should also show two NH stretching bands and since the band at 6.27 μ is only of moderate intensity and in a region where aromatic absorption is also found, we sought stronger confirmatory