The double bond of the 2-amino-5-aryl-4-methyl-2-oxazolines 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-phenylimino-5-phenyloxazolidine (VIIa) reacts with phenyl isocyanate to give 3,4-dimethyl-5-phenyl-2-phenylimino-2-oxazolidine (VIIb).

### Discussion and Results

**Tautomerism.**—The infrared spectral evidence cited 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 NH₂ 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 anomolous 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-oxazolines closely resemble the reported spectra of the 2-amino-4-aryl-2-oxazolines (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 NH₂ 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
evidence that the bands at 2.83, 2.92, and 2.67 μ were due to a primary amino group. We applied the diagnostic test of Boulton and Katritzky\(^5\) for the primary amino group. These authors observed a band at 2.90 μ which appeared between the asymmetric and symmetric stretching bands at 2.86 and 2.95 μ of 5-amino-3-methylisoxazole upon partial deuteration. They ascribe this band to the NH stretch of the NHD group. This provides confirmation that these bands are indeed due to a primary amino group.

When the methyl and phenyl groups are trans to one another on the oxazoline ring, the methine proton at the 4-position occurs at slightly higher field both for 2-amino-2-oxazolines and for 2-iminooxazolines than the corresponding cis compound. The 4-methine resonance is again shifted downfield by about 0.5-0.6 p.p.m. when the double bond is endocyclic. Chemical shifts of 3.98 and 3.80 p.p.m. were observed for the 4-methine protons of VIa and VIc, trans compounds with endocyclic double bonds. For the compound VIIa, which has trans stereochemistry and an exocyclic double bond, a value of 3.27 p.p.m. was observed.

In sharp contrast to 5-phenyl-2-phenylimino-4-oxazolidinone (III),\(^{13}\) 2-anilino-4-methyl-5-phenyl-2-oxazoline (VIIa) exists in the amino form rather than the imino form. The 4-methine proton of VIIa appears at 4.00 p.p.m. while it is found at 3.42 p.p.m. in the spectrum of 3,4-dimethyl-5-phenyl-2-phenyliminooxazoline (VIIb).

The 2-methylenamino compound VIIb also exists in the amino form since it exhibits this resonance at 3.97 p.p.m. vs. 3.27 p.p.m. for the corresponding imino compound VIIa.

The ultraviolet spectra of VIIa and the model compounds VIa and VIIb gave no useful information about the tautomerism of VII since the absorption maxima of all three fell within the range 245-247 m.μ.

Chapman and King\(^7\) have observed coupling of hydroxyl protons with protons on neighboring carbon in dimethyl sulfoxide solution. An attempt to observe coupling between the proton on nitrogen and the protons on the methyl group of the methylamino compound (VIIb) in dimethyl sulfoxide solution was unsuccessful.

The coupling constant between the methine protons at the 4- and 5-positions is also dependent on the position of the double bond. When the substituents are cis, the coupling constant changes from 8 c.p.s. for the exocyclic to 10 c.p.s. for the endocyclic compound. When the substituents are trans, the exocyclic compounds have coupling constants of 9.0 to 9.5 c.p.s. while the endocyclic compounds range from 7 to 8 c.p.s. These changes probably represent a greater deviation from ring planarity in the exocyclic compounds.

Application of the revised Karplus equation\(^4\) would give dihedral angles between methine protons in the cis case of 0° for the endocyclic and 26° for the exocyclic compounds. In the trans case, the angles would vary from 131-134° for the endocyclic compounds to 138-140°.


for the exocyclic compounds. While the magnitude of these angular variations may be subject to large error, the direction of angular variations is probably correct.

The effect of these coupling constants on the patterns of the 4-methine protons is that, when coupling between 4- and 5-methine protons is close to the coupling (about 7.28 p.p.s.) between the 4-methylene and methyl protons, a quintet is observed. When the coupling constants are dissimilar, an eight-line ARX3 pattern is found. Thus the exocyclic cis compounds and the endocyclic trans compounds show a quintet, while the exocyclic trans compounds and endocyclic cis compounds show two overlapping quartets.

**Stereochecmy.**—The aminooxazolines and iminooxazolidines under discussion are prepared by different routes. An amino alcohol (VIII) can be cyclized directly with cyanogen bromide to give the aminooxazoline or iminooxazolidine with retention of configuration. Alternatively, the amino alcohol is converted to a hydroxyurea (IX or X) and the hydroxyurea is cyclized by the action of thionyl chloride and subsequent closure must be almost completely stereospecific in these cases.

The n.m.r. spectra of cis- (IV) and trans-aminooxazoline (VIIa) prepared from amino alcohols of known stereochecmy by the cyanogen bromide route were compared. The trans compound exhibited a methyl peak at 1.36 p.p.m. and 5-methine resonance at 4.95 p.p.m. In the cis compound these peaks were shifted to 0.70 and 5.60 p.p.m., respectively. The origin of these shifts probably arises from a steric interaction between the methyl and phenyl groups of the cis compound which causes the phenyl ring to prefer a conformation perpendicular to the plane best described by the methyl carbon, the carbons at positions 4 and 5, and the 1-carbon of the phenyl ring. Examination of a Dreiding model of IV in this conformation showed that the methyl group would be above the phenyl ring and the 5-methine proton would lie close to the plane of the phenyl ring. Qualitative evaluation of the expected shift using the "isoshielding plot" of Johnson and Bovey showed that the methyl group would be in the region shielded, and the 5-methine proton in the region deshielded, by the phenyl group.

The n.m.r. spectra of the compounds (VIIb-e, VIIa, and X) prepared from erythro amino alcohols by the hydroxyurea route compared well with the trans-aminooxazoline VIIa, prepared by the stereochemically unequivocal cyanogen bromide route. The chemical shifts of the C-methyl groups of compounds VIIb-e and VIIa range from 1.26 to 1.41 p.p.m. and the 5-methine protons from 4.78 to 5.00 p.p.m. No traces of bands were found below 1 or above 5 p.p.m.; therefore, the thionyl chloride reaction and subsequent closure must be almost completely stereospecific in these cases.

**Chemical Reaction.-** In the course of the preparation of 3,4-dimethyl-2-methylimino-5-phenyloxazoline (VIIa), a band at 3.0 μ in the infrared spectrum of this material was observed. We now attribute this band to water since the substance is quite hygroscopic. In order to test for the presence of a secondary amine, VIIa was allowed to react with phenyl isothiocyanate. A substance was isolated in 55% yield which showed no absorption in the 3-μ region and which proved to be identical with the phenylimino compound VIIb. It is suggested that, in analogy to the cycloaddition reactions of enamines with ketenes, the reaction may proceed through a 1,3-diazetidinethione intermediate (XI).

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\text{NH-CO-NR}_1 \text{R}_3 = \text{CH}_3
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\text{C}_6\text{H}_5=\text{CHOH-CH-CH}_3
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\text{NH-CO-NR}_1 \text{R}_3 = \text{CH}_3
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\text{C}_6\text{H}_5=\text{CHOH-CH-CH}_3
\]

**Experimental**

**General.-** The infrared spectra in chloroform were obtained on a Perkin-Elmer Model 21 spectrophotometer. The high-resolution infrared spectra in deuteriochloroform were obtained with a Perkin-Elmer Model 521 spectrophotometer. The ultraviolet spectra were measured with a Cary Model 14 spectrophotometer. The n.m.r. spectra were observed in deuteriochloroform solution using a Varian A-60 instrument. The melting points are corrected. Compounds IV, V, VIa-d, and VIIb have been previously described.

**di-trans-4-Methyl-2-N-methylamino-5-phenyl-2-oxazoline (VIIa)**—A solution of 11.3 g. (0.067 mole) of methylphenylcarbamyl chloride in 100 ml. of chloroform was added to the suspension made by adding 12.5 g. (0.067 mole) of norephedrine hydrochloride (Fisher Chemical Co.) to 67 ml. (0.20 mole) of 12% sodium hydroxide solution. The mixture was stirred at ice-bath temperature for 4 hr. The layers were separated and the aqueous layer was extracted with chloroform. The combined organic solutions were washed with saturated brine and dried over magnesium sulfate. The solvent was evaporated under reduced pressure and 17.8 g. (92% of white crystalline dl-erythro-1-(β-hydroxy-a-methylphenethyl)-3-methyl-3-phenylurea

(IXa) remained. It melted at 114–115° after recrystallization from benzene.

The entire crop of IXa (17.8 g., 0.063 mole) was dissolved in 100 ml. of chloroform and a solution of 4.50 ml. (0.063 mole) of thiolyl chloride in 50 ml. of chloroform was added. The resulting solution was heated for 3 hr. under reflux. The solvent was evaporated under reduced pressure leaving a semisolid mass. Boiling water was admitted to the flask and the mixture was agitated for a few seconds. The aqueous solution was decanted from the residual oil and quickly cooled. The solution was washed with ether and the ether was discarded. The solution was made basic by the addition of concentrated potassium carbonate solution and the mixture was extracted several times with methylene chloride. The methylene chloride solution was dried over magnesium sulfate and evaporated to a cloudy, colorless oil. The oil was distilled through a short Vigreux column; the material began to boil at 153° (0.30 mm.) and the fraction boiling at 155–156° (0.30 mm.) was collected, yield 8.0 g. (48%).

Anal. Calcd. for C17H18N2O: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.60; H, 7.11; N, 10.68.

5,6-Dihydro-4H-1,3,4-thiadiazines

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Treatment of 2-(4-hydroxyalkyl)carboxylic acid hydrazides with phosphorus pentasulfide gave substituted 5,6-dihydro-4H-1,3,4-thiadiazines. The scope of this reaction has been explored. cis and trans isomers have been synthesized and their conformation has been proposed on the basis of n.m.r. data. The mechanism of the reaction is discussed.

As part of a continuing program of exploratory research in heterocyclic chemistry, we turned our attention to the 5,6-dihydro-4H-1,3,4-thiadiazine system.

A survey of the literature showed that Hull, during an investigation of carbohydrate derivatives of alkyl dithiocarbazates, reported that d-glucosamine and methyl dithiocarbazate reacted abnormally to give a product which, on the basis of elemental analysis, could be I.