(12) S. H. Liggero, R. Sustmann, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **91**, 4571 (1969).
(13) Z. Majerski and K. Mlinarić, *Chem. Commun.*, 1030 (1972).
(14) J. E. Nordlander, S. P. Jindal, P. v. R. Schleyer, R. C. Fort, Jr., J. J. Harper, and R. D. Nicholas, *J. Amer. Chem. Soc.*, **88**, 4475 (1966).
(15) A. G. Yurchenko, F. N. Stepanov, S. S. Isaeva, B. M. Zolotarev, V. I. Kadentsev, and O. S. Chizhov, *Org. Mass Spectrom.*, **3**, 1401 (1970); *Chem. Abstr.*, **77**, 34033t (1972).
(16) 1-Homoadamantanol was also prepared by catalytic reduction of 1-hydroxy-4-homoadamantene (**12**) formed in a poor yield by the reaction of 1-hydroxy-4-homoadamantanone tosylhydrazone with *n*-butyllithium. **12** had mp 250–252°; mass spectrum *m/e* (rel intensity) 164 (M^+, 100), 106 (46), 95 (62); ir (KBr) 3300, 1060, 890, 755, 720 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.4–1.8 (11 H, m), 2.47 (3 H, broad s), 6.03 (2 H, dd, J = 6.1, 3.5 Hz).
(17) The reproducibility was about ±10% of the reported values; such an error should be expected since the reaction mixtures were heterogeneous.
(18) R. C. Fort, Jr., and P. v. R. Schleyer, *Advan. Alicycl. Chem.*, **1**, 283 (1966).
(19) The exception is, of course, hydride shift between the positions 4 and 5.
(20) Z. Majerski, P. v. R. Schleyer, and A. P. Wolf, *J. Amer. Chem. Soc.*, **92**, 5731 (1970); P. v. R. Schleyer, L. K. M. Lam, D. J. Raber, J. L. Fry, M. A. McKervey, J. R. Alford, B. D. Cuddy, V. G. Keizer, H. W. Geluk, and J. L. M. A. Schlatmann, *ibid.*, **92**, 5246 (1970), and references cited therein.
(21) R. C. Fort, Jr., in "Carbonium Ions," Vol. 4, G. A. Olah and P. v. R. Schleyer, Ed., Wiley-Interscience, New York, N. Y., 1972, Chapter 32, and references cited therein.
(22) This mechanism is supported by an increase of the ratio **5**:**4** with reaction time observed with all three alcohols (**1**, **2**, and **6**). In the very beginning of the reaction this ratio was found to be lower than one in the case of **1** but higher than one in the cases of **2** and **6**.
(23) G. A. Olah and G. Liang, *J. Amer. Chem. Soc.*, **95**, 194 (1973).
(24) (a) E. Osawa, Z. Majerski, and P. v. R. Schleyer, *J. Org. Chem.*, **36**, 205 (1971); (b) Z. Majerski, A. P. Wolf, and P. v. R. Schleyer, *J. Label. Compounds*, **6**, 179 (1970).
(25) *Cf.* P. v. R. Schleyer, E. Funke, and S. H. Liggero, *J. Amer. Chem. Soc.*, **91**, 3965 (1969).
(26) *Cf.* D. Škare and Z. Majerski, *Tetrahedron Lett.*, 4887 (1972).

Synthesis of Unsaturated Azlactones from *N*-Acylamino Acids

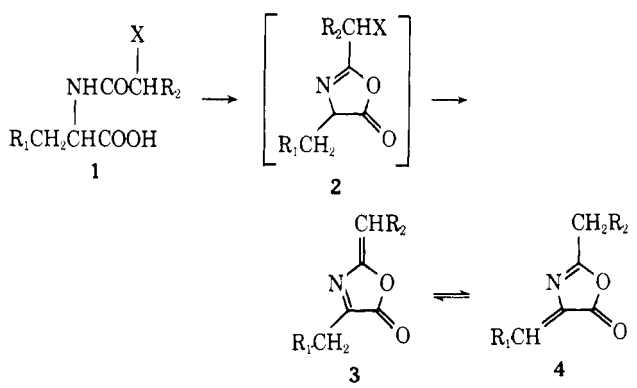
James M. Riordan and Charles H. Stammer*

Department of Chemistry, University of Georgia, Athens, Georgia 30602

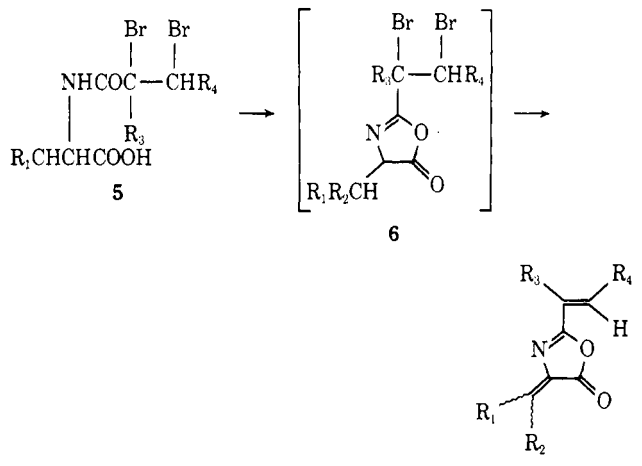
Received August 3, 1973

Phenylalanine, tyrosine, valine, leucine, and isoleucine have been converted to their *N*-(α-methylcinnamoyl) derivatives (**8**). Azlactonization followed by bromine oxidation gave the corresponding unsaturated azlactones (**7**). The configuration about the newly formed double bond was established by nmr correlations, the *Z* configuration being predominant. The mechanism of the double dehydrobromination steps is discussed.

The Bergmann reaction,[1] in which an *N*-(α-haloacyl)-amino acid (**1**) is converted by an acetic anhydride–pyridine mixture into a pseudo-azlactone (**3**), has been known for many years. Several workers[2] have shown that an equilibrium between **3** and the "unsaturated" azlactone **4** can be established and that the position of this equilibrium is determined by the structures of R_1 and R_2 and the conditions[2c,3] under which the reaction is carried out. Our recent communication[4] outlined a procedure making use of an extension of the Bergmann reaction to produce "dehydro" amino acid derivatives without the necessity for equilibration. Treatment of an *N*-α,β-dibromoacylamino acid (**5**) in acetic anhydride at room temperature gave, presumably, the saturated azlactone **6** which was *doubly* dehydrobrominated upon the addition of pyridine to give the unsaturated azlactone **7**. It is the purpose of this paper to describe this work more completely.

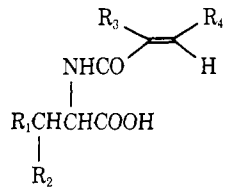


Our initial experiments were carried out on the *N*-(DL-*erythro*-2,3-dibromo-2-methylbutanoyl)-L-phenylalanine (**5a**), which was prepared by a Schotten–Baumann acylation of L-phenylalanine with the dibromoacyl chloride. The derivative, **5a**, was, surprisingly, a sharply melting crystalline solid, even though it was necessarily a mixture of diastereomers. We chose this acyl group because it was readily obtained by bromination of commercially available tiglic acid and we envisioned a necessity for the α-methyl group (R_3 = CH_3) to prevent a possible dehydrobromination of the 2-dibromoalkyl group in **6** since this would, of course, disallow the formation of **7**. A 93% yield[5] of crystalline **7a** was isolated when **5a** was dissolved in acetic anhydride and treated with somewhat more than 2 molar equiv of pyridine. In order to confirm the structure of **7a**, it was prepared by Erlenmeyer[6] condensation of benzalde-



	R_1	R_2	R_3	R_4
a	C_6H_5	H	CH_3	CH_3
b	C_6H_5	H	CH_3	C_6H_5
c	*p*-$AcOC_6H_4$	H	CH_3	C_6H_5
d	CH_3	CH_3	CH_3	C_6H_5
e	CH_3	CH_3CH_2	CH_3	C_6H_5
f	$(CH_3)_2CH$	H	CH_3	C_6H_5
g	C_6H_5	H	H	C_6H_5
h	CH_3	CH_3	H	C_6H_5

Table I
***N*-Acylamino Acids**[a]



8

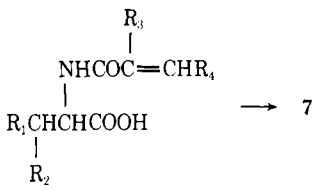
Compd	Mp, °C	Yield,[b] %	Solvent for crystn
8b	154.5–156	90	MeOH–H_2O (1:1)
8c	162–164	72	MEK–petroleum ether (5:1.5)
8f	115–116	87	EtOAc
8d	136–137.5	78	$CHCl_3$–petroleum ether (1:1)
8e	95–99	59[d]	EtOAc–petroleum ether (1:1)
8g[c]	198–199.5	75	MeOH–H_2O (1:1)
8h[c]	187–188	77	EtOAc

[a] Satisfactory analytical data (±0.4% for C, H, N) were reported for all new compounds listed in the table. [b] Yield of recrystallized product. [c] E. Ronwin, *J. Org. Chem.*, **18**, 1546 (1953). [d] Prepared by Mr. Edward Breitholle.

hyde with *N*-tigloylglycine in 26% yield. The identity of these two structures not only established the gross structure of **7a** but gave some insight into its configuration and mechanism of formation in our reaction. The fact that the configuration of the *cis*-2-butenyl group at the 2 position of the azlactone ring was identical in both products indicates that the halogen atoms were eliminated from **6a** in the same trans manner as they were added to the tiglic acid moiety.

When the same sequence of reactions was carried out using DL-leucine, an amorphous unsaturated azlactone was formed. Since we were interested in developing a general method of dehydro amino acid synthesis which would proceed through crystalline intermediates, we changed the acyl group in **5** to the *erythro*-DL-α-methyl-2,3-dibromohydrocinnamoyl function (R_3 = CH_3; R_4 = Ph). Bromination of (*E*)-α-methylcinnamic acid[7] gave the dibromo acid[8] which, after conversion to its acid chloride, was coupled with DL-phenylalanine giving **5b**. Treatment of **5b** with the acetic–pyridine a reagent at room temperature gave the azlactone **7b** in 44% yield. Erlenmeyer synthesis of **7b** in 30% yield from *N*-((*E*)-α-methylcinnamoyl)glycine confirmed the structure of **7b** and again showed that the configurations of both double bonds in the products of these two completely different types of reactions were identical. When the dibromo compound **5b** was also treated with *N,N*-dicyclohexylcarbodiimide, a solution of the intermediate saturated azlactone **6b** (C=O absorption, 1830 cm^{-1}) was obtained which afforded **7b** in 62% yield when treated with pyridine. This confirmed the formation of **6b** and its base-catalyzed dehydrobromination to **7b**.

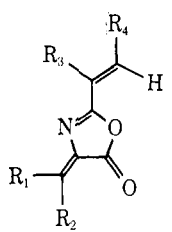
An important simplification of the oxidation procedure was discovered when it was found that a solution of *N*-((*E*)-α-methylcinnamoyl)-DL-phenylalanine (**8b**) in acetic



8

anhydride could be brominated with pyridine perbromide hydrobromide followed by pyridine dehydrobromination to give **7b** in 62% yield. This procedure removed the necessity to prepare the dihaloacylamino acids (**5**) and allowed the unsaturated azlactones to be synthesized directly from the easily prepared α-methylcinnamoylamino acids. Using the appropriate acyl derivatives of tyrosine, valine, isoleucine, and leucine, the azlactones **7c–f** were also prepared. We have subsequently found that the α-methyl group in the cinnamoyl function is unnecessary since the azlactones **7g** and **7h** (R_3 = H) could also be prepared by the direct procedure in acceptable yields. The recrystallized yields and pertinent physical data for the acylamino

Table II
Azlactones[a]

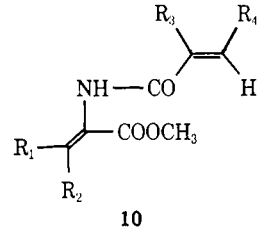


7

Compd	Mp, °C	Yield,[b] %	Solvent for crystn	Nmr, δ
7b	120.5–121	44[c] 62[d]	MeOH–H_2O (3:1)	R_2 = 7.04
7c	163–165	59[d]	Benzene–cyclohexane (3:2)	R_2 = 7.08
7f	83.5–84.5	50[d]	*i*-PrOH	*Z*-R_2 = 6.38 (0.79 H) *E*-R_2 = 6.50 (0.21 H)
7d	138.5–140	63[d]	*i*-PrOH	*Z*-R_1 = 2.32 *E*-R_2 = 2.24
7e	63–67 amorphous	47[d,e]	95% EtOH	*Z*-R_1 = CH_2 = 2.79 R_2 = CH_3 = 2.24 *E*-R_1 = CH_3 = 2.32 R_2 = CH_2 = 2.65
7g	133–134	54[d]	*i*-PrOH	R_2 = 7.08
7h	116–118	24[d]	*i*-PrOH	*Z*-R_1 = 2.30 *E*-R_2 = 2.20

[a] Satisfactory analytical data (±0.4% for C, H, N) were reported for all new compounds listed in the table. [b] Yield after recrystallization. [c] From the dibromoacyl acid. [d] From the cinnamoylamino acid. [e] Prepared by Mr. Edward Breitholle.

Table III
Dehydroamino Acid Methyl Esters[a]



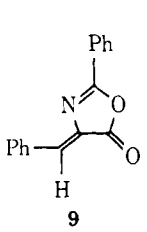
10

Compd	Mp, °C	Yield,[b] %	Solvent for crystn	Nmr, δ
10b	128.5–129.5	83	EtOAc–petroleum ether (2:1)	R_2 = 7.74
10c	109.5–111	52	$CHCl_3$	R_2 = 7.48
(*Z*)-**10f**	108–108.5	77	CCl_4–hexane (1:1)	R_2 = 6.51
(*E*)-**10f**	104–106	57	CCl_4–petroleum ether (1:1)	R_1 = 6.95
10d	98.5–99	93	CCl_4–petroleum ether (1:1)	R_1 = 2.11 R_2 = 1.84
(*Z*)-**10e**	107–108	62[c]	CCl_4–hexane (1:1)	R_1 = CH_2 = 2.49 R_2 = CH_3 = 1.86
(*E*)-**10e**	95–96	73[c]	CCl_4–hexane (1:1)	R_1 = CH_3 = 2.11 R_2 = CH_2 = 2.18
10g	200–201	91	$CHCl_3$–petroleum ether (1:1)	R_2 = 7.73
10h	152–153	82	EtOAc–petroleum ether (3:2)	R_1 = 2.10 R_2 = 1.85

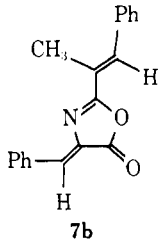
[a] Satisfactory analytical data (±0.4% for C, H, N) were reported for all new compounds listed in the table. [b] Yield after recrystallization. [c] Prepared by Mr. Edward Breitholle.

acids, unsaturated azlactones, and derived esters are reported in Tables I, II, and III, respectively.

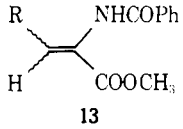
Stereochemistry. The configuration of the new double bond introduced into the carbon chain of the amino acid by the double dehydrobromination reaction should be established if we are to use it later in the synthesis of amino acid derivatives. In 1971, Brocklehurst[9] unequivocally established the *Z* configuration of the 2-phenyl-4-benzylideneazlactone (**9**) prepared by the Erlenmeyer method,



9



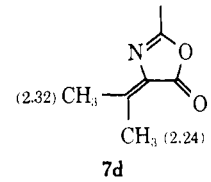
7b



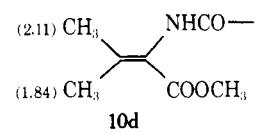
13

using X-ray crystallography. As previously mentioned, the azlactones **7a** and **7b** obtained by our oxidation method were identical with azlactones of the same gross structure prepared by the Erlenmeyer condensation, and should also have the *Z* configuration.[10] Nmr measurements made by Brocklehurst[11a] in 1968, Morgenstern,[10a] and Brown[11b] on the ester **13** derived from both stereoisomers of **9** showed that a vinylic proton cis to the benzamido function in **13** is *downfield* of a proton trans to that function.[12] This key piece of information allowed us to assign the *Z* configuration to azlactones **7a**, **7b**, **7c**, and **7g** and to assign the *Z* configuration to the predominant isomer (79%) of **7f** formed when leucine was oxidized by our procedure. We have no evidence of the formation of more than one isomer when an arylidene azlactone (R_1 = Ar) is the product, but both isoleucine and leucine afforded mixtures of isomers which were separable after conversion to the corresponding methyl esters (**10**) by azlactone methanolysis. Isoleucine gave approximately an equimolar mixture of the *E* and *Z* isomers, while leucine gave a 4:1 *Z*:*E* mixture. This is consistent with the hypothesis that the larger group is favored to take the position cis to the nitrogen atom in the oxazolone ring (*Z* configuration). The *Z* configuration is apparently favored on steric grounds with the larger group taking the least hindered position as discussed by Zimmerman[13] in connection with the Perkin condensation. Isoleucine, having two groups, methyl and ethyl, of approximately the same size, gave about equal amounts of both isomers.

Table IV shows a possible correlation between the change in chemical shift ($\Delta\nu$) of the β-vinylic proton when the azlactone is converted into the corresponding ester and the double bond configuration. Compounds having the *Z* configuration show a smaller downfield shift than those having the *E* configuration in the three cases for which data are available. It may be possible to make assignments on the basis of $\Delta\nu$ as more of these data become available. We can assign the shift positions of the methyl protons in azlactone **7d** and the ester **10d** formed from valine by reference to the elegant work of Brown and Smale,[11b] who deduced the chemical shifts of the methyl protons in methyl α-benzamido-β-methylcrotonate. Referring to the formulas **7d** and **10d**, we see that the $\Delta\nu$ value for

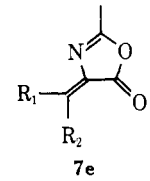


7d



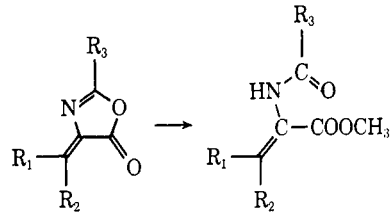
10d

the *Z*-methyl group[14] of **7d** is −0.21 and that of the *E*-methyl group is −0.40. Assuming, then, that an *E*-methyl group[15] will have the larger absolute $\Delta\nu$ value in **7e**, these



7e

Table IV
Correlation of $\Delta\nu$ with Configuration

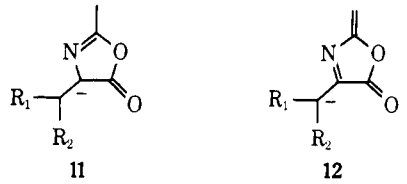


R_1	R_2	R_3	Configuration	$\Delta\nu = \nu_{est} - \nu_{az}$	Ref
3,4-$(CH_3O)_2C_6H_3$	H	C_6H_5	*Z*	0.29[a]	10, 12a
H	3,4-$(CH_3O)_2C_6H_3$	C_6H_5	*E*	0.52[a]	10, 12a
C_6H_5	H	C_6H_5	*Z*	0.20[b]	12a
H	C_6H_5	C_6H_5	*E*	0.32[b]	12a
$(CH_3)_2CH$	H	$C_6H_5CH{=}C(CH_3)$	*Z*	0.08	*c*
H	$(CH_3)_2CH$	$C_6H_5CH{=}C(CH_3)$	*E*	0.40	*c*
Z-CH_3	*E*-CH_3	$C_6H_5CH{=}C(CH_3)$		*Z*-CH_3 −0.21	*c*
				E-CH_3 −0.40	*c*
CH_3[d]	C_2H_5	$C_6H_5CH{=}C(CH_3)$	*E*	−0.21	*c*
C_2H_5[d]	CH_3	$C_6H_5CH{=}C(CH_3)$	*Z*	−0.30	*c*

[a] Ethyl esters. [b] Using the centers of broad peaks. [c] This work. [d] Prepared by Mr. Edward Breitholle.

values can be used to assign the configurations of the two azlactones formed from isoleucine. The isomer of **7e** which shows the larger methyl group $\Delta\nu$ value of −0.30 should be the *Z* isomer ($R_1 = C_2H_5$, $R_2 = CH_3$) and the isomer having $\Delta\nu = -0.21$ can be assigned the *E* configuration ($R_1 = CH_3$; $R_2 = C_2H_5$).

Mechanism. The predominance of *Z* isomers in the products of the bromine oxidation, except in the case of isoleucine where R_1 and R_2 are almost sterically equivalent, indicates that the overall process gives the product having the most stable double bond (*Z* configuration) and is stereoselective rather than stereospecific. Since the 1,4-dehydrobromination should give approximately the same mixture of pseudo-azlactones no matter what the sizes of R_1 and R_2, the second step, which determines the final configuration and *is* sensitive to the bulk of R_1 and R_2, must also be stereoselective and most probably nonconcerted. The first step is very likely to be of the E1cb type,[16] since the carbanion **11** at C-4 in the azlactone ring is of considerable stability as evidenced by the well-known ease of racemization of optically active azlactones.[17] The second step is also likely to be of the same mechanistic type, since the requisite carbanion **12** would have considerable resonance stabilization. The formation of these stable carbanions should lead to thermodynamic control of configuration and an overall stereoselective process.



11 **12**

Experimental Section

General. The nuclear magnetic resonance spectra were recorded on a Varian HA-100 spectrometer with tetramethylsilane as the internal standard and the infrared spectra were obtained on a Perkin-Elmer Model 257 spectrophotometer as Nujol mulls with polystyrene as a standard. Melting points were determined on a Nagle Model Y6 hot stage. Elemental analyses were carried out by Atlantic Microlabs, Atlanta, Ga.

***N*-α-Methylcinnamoyl- and *N*-Cinnamoylamino Acids (8).** A solution of 50 mmol of the acid chloride in 25 ml of 1,2-dimethoxyethane (DME) was added dropwise in 30 min to a solution of 50 mmol of the amino acid in 100 ml of a 1:1 mixture of DME: 1 *N* LiOH in a 300 ml three-necked round-bottomed flask equipped with a magnetic stirrer, delivery funnel, and an electrode attached to a Corning Model 10C pH control unit. The reaction mixture was maintained at pH 10 by the addition of 1 *N* LiOH during the acid chloride addition. After a further 30 min at room temperature, the reaction mixture was cooled with ice and adjusted to pH 1 with concentrated HCl. The white precipitate was filtered, dried *in vacuo* overnight, and purified by crystallization. If a precipitate did not form, the acidic solution was extracted with three 100-ml portions of ethyl acetate, the combined extracts were dried ($MgSO_4$) and evaporated *in vacuo*, and the residue was crystallized.

The yields, melting points, and recrystallization solvents for these *N*-acyl-α-amino acids are given in Table I. Nujol mulls of these acylamino acids showed major absorption bands in the following spectral regions: 1700–1730 (COOH), 1635–1660 (C=C), 1595–1615 cm^{-1} (amide 1).

Azlactones (7). To a solution of 10 mmol of the *N*-acylamino acid in 10 ml of acetic anhydride containing 6 drops of pyridine, 10 mmol of pyridinium hydrobromide perbromide was added. After stirring for 15 min, 3 ml of pyridine was added to the light amber solution and the reaction mixture was stirred for 15 min at room temperature, during which time pyridine HBr precipitated. The mixture was poured into 150 ml of an ice-H_2O mixture, stirred for 30 min, and filtered. The solid obtained was crystallized giving the pure products.

The yields, melting points, recrystallization solvents, and nmr data for these azlactones are given in Table II. Nujol mulls of these azlactones showed major absorption bands in the following spectral regions: 1770–1800 (C=O) with shoulder at 10–20 cm^{-1} lower frequency, 1645–1665 cm^{-1} (C=N).

Dehydro Amino Acid Methyl Esters (10). To a solution of 1 ml of 0.5 *N* sodium methoxide in 50 ml of absolute methanol, 15 mmol of the azlactone was added. After stirring for 30 min at room temperature, the pH of the reaction solution was adjusted to 3 with concentrated HCl. The solvent was evaporated *in vacuo*, the crude residue was dissolved in 50 ml of ethyl acetate, and the solution was extracted with two 25-ml portions of H_2O. The ethyl acetate solution was dried ($MgSO_4$) and evaporated *in vacuo* and the residue was crystallized.

The yields, melting points, recrystallization solvents, and nmr data for these dehydro *N*-acylamino esters are given in Table III. Nujol mulls of these esters showed major absorption bands in the following spectral regions: 1710–1730 (ester C=O), 1650–1660 (C=C), 1615–1645 (C=C), 1600–1625 cm^{-1} (amide 1).

Methyl α-((*E*)-α-Methylcinnamamido)-(*Z*)-β-isopropylacrylate [(*Z*)-10f)]. To a solution of 1 ml of 0.5 *N* sodium methoxide in 50 ml of methanol, 2.76 g (10.8 mmol) of crude **7f** was added. After stirring for 15 min at room temperature the pH of the reaction mixture was adjusted to 3 with concentrated HCl. The solvent was evaporated *in vacuo*, giving a crude mixture which was dissolved in 150 ml of ethyl acetate and extracted with two 50 ml-portions of H_2O. The ethyl acetate solution was dried ($MgSO_4$) and evaporated *in vacuo*, giving 2.96 g of a crude mixture of isomers. Crystallization of the mixture from 20 ml of car-

bon tetrachloride and 26 ml of hexane gave 1.91 g (61%) of (*Z*)-**10f**, mp 102–106°. Further recrystallization of (*Z*)-**10f** from 1:1 carbon tetrachloride–hexane gave an analytical sample: mp 108–108.5°; ir (Nujol) 3230 (NH), 1730 ($COOCH_3$), 1655 and 1640 (C=C), 1615 (amide I), 1500 cm^{-1} (amide II); nmr ($CDCl_3$) δ 7.30 [m, 7 H, **PhCH**=C(CH_3)–, NH], 6.51 (d, 1 H, J = 10 Hz, *Z* –CH=C<, 3.72 (s, 3 H, $COOCH_3$), 2.65 [m, 1 H, –**CH**(CH_3)$_2$], 2.11 [s, 3 H, PhCH=C(**CH_3**)–], 1.04 ppm [d, 6 H, J = 7 Hz, CH(**CH_3**)$_2$].

Methyl α-((*E*)-α-Methylcinnamamido)-(*E*)-β-isopropylacrylate [(*E*)-10f]. A 473-mg sample obtained from the mother liquor of (*Z*)-**10f** was chromatographed on a 1.25-cm thick silica gel G plate by elution with $CHCl_3$, giving 214 mg of the crude *E* isomer, which was crystallized from 3:2 CCl_4–petroleum ether (bp 30–60°), yielding 161 mg of (*E*)-**10f**, mp 103–106°. The analytical sample was recrystallized from 1:1 CCl_4–petroleum ether: mp 104–106°; ir (Nujol) 3310 (NH), 1720 ($COOCH_3$), 1655 and 1645 (C=C), 1610 (amide I), 1505 cm^{-1} (amide II); nmr ($CDCl_3$) δ 7.86 (broad s, 1 H, NH), 7.31 [m, 6 H, **PhCH**=C(CH_3)–], 6.95 (d, 1 H, J = 10 Hz, *E* –CH=C<), 3.80 (s, 3 H, $COOCH_3$), 3.31 [m, 1 H, **CH**(CH_3)$_2$], 2.10 [s, 3 H, PhCH=C(**CH_3**)–], 1.06 ppm [d, 6 H, J = 7 Hz, CH(**CH_3**)$_2$].

Methyl α-((*E*))-α-Methylcinnamamido)-β-methyl-2-pentenorate [(*E*)- and (*Z*)-10e].[18] To a suspension of 2.55 g (10 mmol) of **7e** in 50 ml of methanol was added 1.01 ml of 0.48 *N* sodium methoxide and in several minutes the solid dissolved. The reaction course was followed by tlc (1:1 *n*-hexane–$CHCl_3$) and the clear solution was acidified with concentrated HCl to pH 2.5. The solvent was evaporated *in vacuo*, the residue was dissolved in ethyl acetate, and the solution was washed with water, dried ($MgSO_4$), and evaporated *in vacuo*, giving 2.9 g (100%) of **10e**. Recrystallization from 1:1 CCl_4–*n*-hexane yielded 2.46 g (86%) of white crystals: mp 82–84°; ir (Nujol) 3275 (NH), 1728 ($COOCH_3$), 1640 (amide I), 1618 cm^{-1} (C=C); nmr ($CDCl_3$) 1.08 (2 t, 3 H, **CH_3**CH_2), 1.81 (s, 3 H, CH_3CH_2(**CH_3**)C=), 2.18 [s, 3 H, PhCH=C(**CH_3**)–], 2.15–2.6 (m, 2 H, CH_2), 3.68 (s, 3 H, $COOCH_3$), 7.30 (s, 5 H, Ph), 7.38 (s, 1 H, PhC**H**=), 7.97 ppm (m, 1 H, NH).

A 600-mg sample of the above product was separated by preparative chromatography using 2.5-mm silica gel plates eluted with 8.5:1.5 *n*-hexane–acetone. The plates were developed 13 times yielding two bands at R_f 0.40 and 0.45. Crystallization from 1:1 CCl_4–*n*-hexane yielded 219 mg of (*E*)-**10e**: mp 95–96°; ir (Nujol) 3238 (NH), 1712 ($COOCH_3$), 1640 (amide I), 1614 cm^{-1} (C=C); nmr ($CDCl_3$) 1.00 (t, 3 H, **CH_3**CH_2), 2.11 [s, 6 H, PhCH=C(**CH_3**)–, CH_3CH_2(**CH_3**)C=], 2.18 (q, 2 H, CH_2), 3.69 (s, 3 H, $COOCH_3$), 7.30 (s, 5 H, Ph), 7.34 (s, 1 H, PhC**H**=), 7.52 ppm (m, 1 H, N**H**), and 180 mg (*Z*)-**10e**: mp 107–108°; ir (Nujol) 3220 (NH), 1717 ($COOCH_3$), 1637 (amide I), 1612 cm (C=C); nmr ($CDCl_3$) 1.11 (t, 3 H, **CH_3**CH_2), 2.49 (q, 2 H, CH_2), 1.86 [s, 3 H, PhCH=O(**CH_3**)–], 2.12 [s, 3 H, CH_3CH_2(**CH_3**)C=], 3.72 (s, 3 H, $COOCH_3$), 7.32 (s, 5 H, Ph), 7.36 (s, 1 H, PhC**H**=), 7.45 ppm (m, 1 H, NH).

***N*-(DL-*erythro*-2,3-Dibromo-2-methylbutanoyl)-L-phenylalanine (5a).** A solution of 9.02 g (54.5 mmol) of L-phenylalanine in 150 ml of 10% sodium bicarbonate in a three-necked flask equipped with magnetic stirred and delivery funnel was cooled in an ice bath and 11.75 g (42.5 mmol) of DL-*erythro*-2,3-dibromo-2-methylbutanoyl chloride was added dropwise over a 30-min period. After stirring for 2 hr, the ice bath was removed and the reaction mixture was stirred for another 3 hr at room temperature. The pH of the reaction mixture was adjusted to 1 with concentrated HCl and it was extracted with four 150-ml portions of ethyl ether. The combined extracts were dried (Na_2SO_4) and the ether was evaporated *in vacuo*, giving 15.79 g (90%) of crude **5a**. Crystallization of the crude product from ethyl acetate–petroleum ether gave 13.84 g (81%) of **5a**: mp 116.5–117°; ir (Nujol) 3330 (NH), 1715 (C=O), 1655 (amide I), 1554 cm^{-1} (amide II); nmr ($CDCl_3$) δ 1.68 (d, 3 H, **CH_3**CHBr–, J = 6 Hz), 1.88 (d, 3 H, **CH_3**CHBr–, J = 6 Hz), 1.91 [s, 3 H, –C(**CH_3**)Br–], 1.96 [s, 3 H, –C(**CH_3**)Br–], 3.20 (m, 4 H, **CH_2**Ph), 5.58 (m, 2 H, CH_3**CH**Br–), 5.88 [m, 2 H, –**CH**(COOH)–], 7.20 ppm (s, 10 H, Ph). *Anal.* Calcd for $C_{14}H_{17}NO_3Br_2$: C, 41.30; H, 4.21; N, 3.44 Found: C, 41.48; H, 4.24; N, 3.48.

***N*-Tigloylglycine.** A solution of 3.28 g (27.8 mmol) of tigloyl chloride (prepared from 5.0 g of tiglic acid using $SOCl_2$) in 20 ml of tetrahydrofuran was added in 2-ml increments to a solution of 6.45 g (86 mmol) of glycine in 100 ml of 10% aqueous sodium bicarbonate solution contained in a separatory funnel. After the reaction was complete the pH was adjusted to 2 with concentrated HCl and the solution was saturated with NaCl and extracted with three 100-ml portions of ethyl ether. The combined extracts were dried (Na_2SO_4) and the ether was evaporated *in vacuo*, giving 2.51 g (58%) of crude product. Crystallization of the crude product from 1:1 $CHCl_3$–CCl_4 gave 1.69 g (67%) of *N*-tigloylglycine: mp 86.5–88°; ir (Nujol) 3420 (NH), 1705 (COOH), 1665 (C=C), 1585 (amide I), 1535 cm^{-1} (amide II); nmr ($CDCl_3$) δ 6.81 (t, 1 H, NH), 6.57 (q, 1 H, vinyl H), 4.08 (d, 2 H, J = 6 Hz, $-CH_2-$), 1.84 (s, 3 H, CH_3-), 1.75 ppm (d, 3 H, **CH_3**CH=). *Anal.* Calcd for $C_7H_{11}NO_3$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.52; H, 7.11; N, 8.91.

***N*-((*E*)-α-Methylcinnamoyl)glycine.** A solution of 4.50 g (25 mmol) of (*E*)-α-methylcinnamoyl chloride in 25 ml of DME was added dropwise over a 1-hr period to a solution of 3.78 g (50 mmol) of glycine in 25 ml of 2 *N* LiOH and 25 ml of DME in a 100-ml three-necked flask equipped with a magnetic stirrer and a delivery funnel. The DME was evaporated *in vacuo* and the pH of the cooled reaction mixture was adjusted to 1 with concentrated HCl and extracted with two 100-ml portions of ethyl acetate. The combined extracts were washed with two 50 ml-portions of H_2O and dried (Na_2SO_4) and the solvent was evaporated *in vacuo*, giving 4.81 g (90%) of *N*-((*E*)-α-methylcinnamoyl)glycine. Crystallization from ethyl acetate gave 4.22 (77%) of white needles: mp 140–141°; ir (Nujol) 3330 (NH), 1755 and 1735 (COOH), 1630 (C=C), 1585 cm^{-1} (amide I); nmr (TFA) δ 8.00–7.60 (broad s, 1 H, NH), 7.58 (s, 1 H, PhC**H**=), 7.37 (s, 5 H, Ph), 4.45 (s, 2 H, $-CH_2-$), 2.21 ppm (s, 3 H, CH_3). *Anal.* Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.51; H, 6.03; N, 6.44.

***N*-(DL-*erythro*-α-Methyl-2,3-dibromohydrocinnamoyl)-DL-phenylalanine (5b).** A solution of 5.43 g (15.9 mmol) of DL-*erythro*-2,3-dibromo-2-methyl-3-phenylpropanoyl chloride in 14 ml of DME was added dropwise in 1 hr to a solution of 4.51 g (32.8 mmol) of DL-phenylalanine in 160 ml of 5% sodium bicarbonate in a three-necked flask equipped with a magnetic stirrer and delivery funnel. After stirring for 1 hr at room temperature, the reaction mixture was cooled, its pH adjusted to 1 with concentrated HCl, and extracted with three 125-ml portions of ethyl ether. The combined extracts were dried (Na_2SO_4) and evaporated *in vacuo*, giving 5.93 g (80%) of **5b** as an amorphous solid. A solution of the amorphous solid in 10 ml of ethyl acetate was added dropwise to a stirred solution of 3000 ml of petroleum ether, giving a white precipitate; mp 161–167°; ir ($CHCl_3$) 3390 (NH), 1730 (COOH), 1670 (amide I), 1500 cm^{-1} (amide II).

Methyl α-(Tiglamido)-*trans*-cinnamate (10a). To a solution of 1 ml of sodium methoxide in 20 ml of absolute methanol 1.36 g (5.99 mmol) of **7a** was added. After stirring for 15 min at room temperature the pH of the solution was adjusted to 2 with concentrated HCl. The solvent was evaporated *in vacuo*, giving a crude mixture which was dissolved in 40 ml of ethyl acetate, and the solution was extracted with two 25-ml portions of H_2O. The ethyl acetate solution was dried ($MgSO_4$) and the solvent was evaporated *in vacuo*, giving 1.46 g (94%) of methyl α-(tiglamido)-*trans*-cinnamate, mp 117–119°. Crystallization from 1:2 ethyl acetate–petroleum ether gave 1.36 g (88%) of an analytical sample: mp 117.5–119°; ir (Nujol) 3230 (NH), 1710 ($COOCH_3$), 1658 (C=C), 1620 (amide I), 1488 cm^{-1} (amide II); nmr ($CDCl_3$) δ 7.50 (s, 1 H, PhCH=), 7.26 (m, 6 H, **PhCH**=, NH), 6.46 (q, 1 H, J = 7 Hz, CH_3**CH**=), 3.70 (s, 3 H, $COOCH_3$), 1.81 [s, 3 H, CH_3CH=C(**CH_3**)–], 1.72 ppm (d, 3 H, J = 7 Hz, **CH_3**CH=). *Anal.* Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.63; H, 6.66; N, 5.33.

2-(*cis*-2-Butenyl)-4-benzylidene-2-oxazolin-5-one (7a). A. From *N*-(DL-*erythro*-2,3-Dibromo-2-methylbutanoyl)-L-phenylalanine (5a). Pyridine (15 ml) was added to a solution of 6.17 g (15.1 mmol) of **5a** in 95 ml of acetic anhydride. After stirring for 30 min at room temperature, the reaction mixture was filtered and poured into 250 ml of anhydrous ethyl ether. The slurry was filtered and the filtrate was evaporated *in vacuo*, giving 4.67 g of an amorphous solid. Crystallization from 5:1 methanol–water gave 3.18 g (93%) of **7a**, mp 115–116°. Recrystallization from methanol–water gave an analytical sample: mp 116–116.5°; ir (Nujol) 1785 (C=O), 1650 (C=N), 1620 cm^{-1} (C=C); nmr (CCl_4) δ 8.02 (m, 2 H, ortho H's of Ph), 7.32 (m, 3 H, Ph), 6.96 (s, 1 H, =C**H**Ph), 6.83 (q, 1 H, J = 6.5 Hz, CH_3**CH**=), 2.04 [s, 3 H, –(CH_3)C=], 1.90 ppm (d, 3 H, J = 6.5 Hz, **CH_3**CH=). *Anal.* Calcd for $C_{14}H_{13}NO_2$: C, 73.99; N, 5.77; N, 6.16. Found: C, 74.07; H, 5,83; N, 6.20.

B. From *N*-Tigloylglycine. A solution of 550 mg (3.5 mmol) of *N*-tigloylglycine, 200 mg (2.44 mmol) of fused sodium acetate, 550 mg (5 mmol) of benzaldehyde, and 6 ml of acetic anhydride was refluxed for 2 hr. The solvent was evaporated *in vacuo*, giving an amorphous solid which was washed with 5% sodium bicarbonate

and water and crystallized from 6:1 methanol-water giving 417 mg (52%) yellow solid, mp 103–114°. Recrystallization from methanol-water gave 208 mg (26%) of **7a**, yellow needles, mp 116–117°, identical in all respects with product obtained by method A.

C. From *N*-Tigloyl-DL-phenylalanine (8a). A 1.31-g (4.12 mmol) portion of pyridine hydrobromide perbromide was added to a solution of 1.02 g (4.12 mmol) of **8a** in 20 ml of acetic anhydride containing 1 drop of pyridine. The solution was stirred until the reddish-brown solution turned canary yellow. Pyridine (3 ml) was added and the reaction mixture was stirred for 15 min at room temperature. The slurry was poured into 200 ml of ice and H_2O and the mixture was stirred for 30 min and filtered. The precipitate was dried *in vacuo* and the brown solid was crystallized from 1:2 ethyl acetate-petroleum ether, giving 0.63 g (68%) of **7a**, mp 114–115°. Recrystallization from isopropyl alcohol gave 0.50 g (50%) of **7a**, mp 116–116.5°, identical in all respects with product obtained by method A.

***N*-Tigloyl-DL-phenylalanine (8a).** A solution of 2.49 g (20 mmol) of tigloyl chloride in 20 ml of 1,2-dimethoxyethane (DME) was added dropwise in 30 min to a stirred solution of 1.67 g (40 mmol) of lithium hydroxide and 6.96 g (42 mmol) of DL-phenylalanine in 25 ml of H_2O and 20 ml of DME. The reaction mixture was poured into 100 ml of ice and H_2O and the pH was adjusted to 1 with concentrated HCl. The white precipitate was filtered and dried overnight *in vacuo*, giving 3.90 g (75%) of crude **8a**, mp 132–134°. Crystallization from 1:1 ethyl acetate-petroleum ether gave an analytical sample: mp 132–134°; ir (Nujol) 3320 (NH), 1725 (COOH), 1655 (C=C), 1575 (amide I), 1530 cm^{-1} (amide II); nmr ($CDCl_3$) 7.20 (m, 5 H, Ph), 6.38 (m, 2 H, CH_3CH=, NH), 5.92 (m, 1 H, -CHCOOH-), 3.19, 3.22 (q, 2 H, J = 6 Hz, $PhCH_aH_b$), 1.72 (s, 3 H, CH=CCH_3), 1.68 ppm (d, 3 H, CH_3CH=). *Anal.* Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.86; H, 6.97; N, 5.77.

Preparation of 2-(*cis*-1-Methylstyryl)-4-benzlidene-2-oxazolin-5-one (7b). Method A. From 5b. 1. Using Acetic Anhydride and Pyridine. Pyridine (8 ml) was added to a solution of 2.72 g (5.8 mmol) of **5b** in 45 ml of acetic anhydride. After stirring for 30 min at room temperature, the reaction mixture was poured into 150 ml of an ice-H_2O mixture, stirred for 30 min, and filtered. The yellow precipitate was washed with H_2O and crystallized from 3:1 methanol-water, giving 0.74 g (44%) of **7b**: mp 120.5–121°; ir (Nujol) 1795 and 1775 (C=O), 1645 cm^{-1} (C=N); nmr ($CDCl_3$) δ 8.02 [m, 2 H, 2,6 H's of Ph (R_1)], 7.55 [q, 1 H, J = 3.5 Hz, PhC**H**=C(CH_3)-], 7.38 [m, 8 H, **Ph**CH=C(CH_3)- and Ph]; 7.04 (s, 1 H, PhC**H**=), 2.30 ppm (d, J = 3.5 Hz, 3 H, CH_3). *Anal.* Calcd for $C_{19}H_{15}NO_2$: C, 78.87; H, 5.23; N, 4.84. Found: C, 78.22; H, 5.18; N, 4.84.

2. Using Dicyclohexylcarbodiimide. A solution of 1.77 g (8.6 mmol) of dicyclohexylcarbodiimide in 20 ml of CH_2Cl_2 was added to a solution of 3.88 g (8.3 mmol) of **5b** in 40 ml of CH_2Cl_2. After the reaction mixture was stirred for 3 hr, the dicyclohexylurea was filtered (1.49 g, 78%) and the infrared spectrum of the filtrate showed 1830 (C=O), 1785 (C=O), 1655 cm^{-1} (C=N). Pyridine (4 ml) was added to this solution, which was stirred for 15 min and evaporated *in vacuo*, giving a light yellow solid. The solid was stirred with 100 ml of H_2O, filtered, and dried *in vacuo* overnight, giving 2.71 g of dicyclohexylurea and **7b**. Crystallization from isopropyl alcohol gave 1.49 g (62%) of **7b**, mp 118–120°, spectrally identical with a sample obtained by method A.

Method B. From *N*-((*E*)-α-Methylcinnamoyl)glycine. A solution of 5.89 g (26.8 mmol) of *N*-((*E*)-α-methylcinnamoyl)glycine, 1.72 g (18.6 mmol) of fused sodium acetate, 3.84 ml (37.0 mmol) of benzaldehyde, and 45 ml of acetic anhydride was refluxed for 2 hr. The solvent was evaporated *in vacuo*, giving an amorphous solid which was washed with 5% sodium bicarbonate, water, and methanol, giving a yellow solid which was crystallized from 5:1.5 methanol-water, giving 2.30 g (30%) of **7b**, mp 119–121°, spectrally identical with a sample obtained by method A.

Method C. From *N*-((*E*)-α-Methylcinnamoyl)-DL-Phenylalanine (8b). To a solution of 690 mg (2.23 mmol) of **8b** in 20 ml of acetic anhydride containing 1 drop of pyridine was added 718 mg (2.24 mmol) of pyridine hydrobromide perbromide. After the reaction mixture was warmed to 80°, it was cooled to room temperature and 4 ml of pyridine was added. The reaction mixture was stirred for 10 min at room temperature, during which time a precipitate formed. The mixture was poured into 100 ml of an ice-H_2O mixture, stirred for 30 min, and filtered. The light yellow solid obtained was crystallized from methanol and H_2O, giving 395 mg (62%) of **7b**, mp 121–121.5°, spectrally identical with a sample obtained by method A.

Registry No. 5a, 49659-60-1; **5b,** 49659-61-2; **7a,** 49659-62-3; **7b,** 49659-63-4; **7c,** 49659-64-5; **7d,** 49659-65-6; **7e** (R, Me *Z* to N), 49659-66-7; **7e** (R, Me *E* to N), 49659-67-8; **7f,** 49659-68-9; **7g,** 49659-69-0; **7h,** 49659-70-3; **8a,** 49659-71-4; **8b,** 49659-72-5; **8c,** 49659-73-6; **8d,** 49659-74-7; **8e,** 49659-75-8; **8f,** 49659-76-9; **8g,** 49659-77-0; **8h,** 49659-78-1; **10a,** 49659-79-2; **10b,** 49659-80-5; **10c,** 49659-81-6; **10d,** 49659-82-7; (*Z*)-**10e,** 49659-83-8; (*E*)-**10e,** 49659-84-9; (*Z*)-**10f,** 49659-85-0; (*E*)-**10f,** 49659-86-1; **10g,** 49659-87-2; **10h,** 49659-83-3; L-phenylalanine, 63-91-2; DL-*erythro*-2,3-dibromo-2-methylbutanoyl chloride, 49659-89-4; *N*-tigloylglycine, 35842-45-6; tigloyl chloride, 35660-94-7; glycine, 56-40-6; *N*-((*E*)-α-methylcinnamoyl)glycine, 49659-92-9; (*E*)-α-methylcinnamoyl chloride, 38449-13-7; DL-*erythro*-2,3-dibromo-2-methyl-3-phenylpropanoyl chloride, 49659-94-1; DL-phenylalanine, 150-30-1; dicyclohexylcarbodiimide, 538-75-0.

References and Notes

(1) M. Bergmann and F. Stern, *Justus Liebigs Ann. Chem.*, **448,** 20 (1926).
(2) (a) J. C. Sheehan and W. E. Duggins, *J. Amer. Chem. Soc.*, **74,** 2475 (1950); (b) Y. Iwakura, F. Toda, and Y. Torii, *Tetrahedron*, **23,** 3363 (1967); (c) W. Steglich and R. Hurmans, *Tetrahedron Lett.*, 383 (1966).
(3) H. Kurita, Y. Chigira, M. Masaki, and M. Ohta, *Bull. Chem. Soc. Jap.*, **41,** 2758 (1968).
(4) J. M. Riordan and C. H. Stammer, *Tetrahedron Lett.*, 4969 (1971).
(5) The crude yields of the azlactones prepared in our work were all 70–90%.
(6) E. Erlenmeyer, Jr., *Justus Liebigs Ann. Chem.*, **337,** 283, 294, 302 (1904).
(7) J. R. Johnson in "Organic Reactions," Vol. 1, R. Adams, Ed., Wiley, New York, N. Y., 1942, p 251.
(8) M. Conrad and W. R. Hodgkinson, *Justus Liebigs Ann. Chem.*, 193, 316 (1878).
(9) K. Brocklehurst, R. P. Bywater, R. H. Plainer, and R. Patrick, *Chem. Commun.*, 632 (1971).
(10) (a) A. P. Morgenstern, C. Schutsi, and W. T. Nauta, *Chem. Commun.*, 632 (1971); (b) K. R. Hanson, R. H. Wightman, J. Stanton, and A. R. Battersby, *ibid.*, 185, (1971).
(11) (a) K. Brocklehurst, H. S. Price, and K. Williamson, *Chem. Commun.*, 884 (1968); (b) A. G. Brown and T. C. Smale, *ibid.*, 1489 (1969).
(12) This was contrary to the earlier assumptions made by Brocklehurst which had led him to make incorrect configurational assignments prior to his X-ray work in 1971.
(13) H. E. Zimmerman and L. Ahramjian, *J. Amer. Chem. Soc.*, **81,** 2086 (1959).
(14) *E*- and *Z*-methyl groups are trans and cis to the nitrogen atom, respectively.
(15) The isomer of **7e** with an *E*-methyl group has the *Z* configuration and, conversely, that having a *Z*-methyl group has the *E* configuration.
(16) D. J. McLennan, *Quart. Rev., Chem. Soc.*, **21,** 490 (1967).
(17) (a) M. Goodman and W. J. McGahren, *Tetrahedron*, **23,** 2031 (1967); (b) M. Goodman and L. Levine, *J. Amer. Chem. Soc.*, **86,** 2918 (1964).
(18) This experiment was carried out by Mr. Edward Breitholle in our laboratories.