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The Total Synthesis of the Alkaloid Casimiroedine, an Imidazole Nucleoside[1a]

Raymond P. Panzica and Leroy B. Townsend*

Contribution from the Department of Chemistry and Department of Biopharmaceutical Sciences, University of Utah, Salt Lake City, Utah 84112. *Received August 16, 1973*

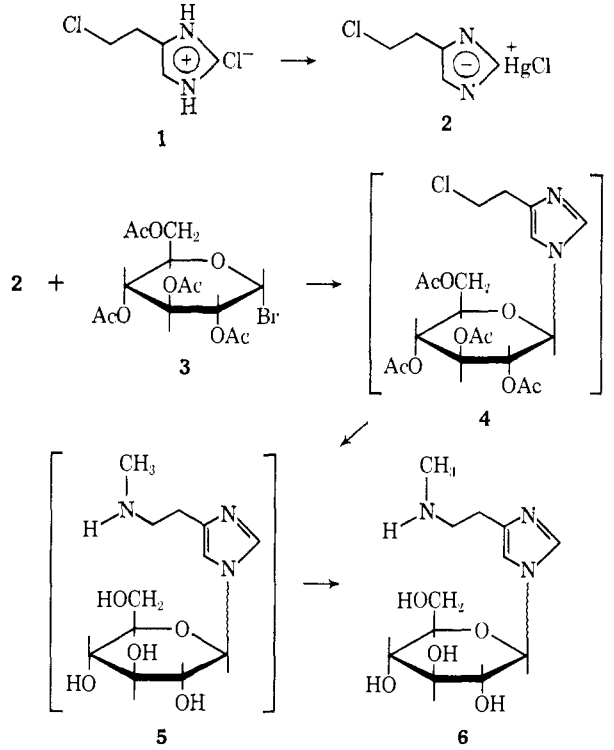
Abstract: The syntheses of the imidazole alkaloid casimiroedine (**7**), a natural product isolated from the seeds of the Mexican fruit "Zapote blanco," and its hydrolysis product casimidine (**6**) have been accomplished. The key step in the synthesis of casimiroedine (**7**) involves the formation of the peptide linkage between *trans*-cinnamic acid and casimidine. The unambiguous synthesis of **7** established the stereochemistry of the cinnamoyl moiety as trans. This assignment was corroborated by the synthesis of *cis*-casimiroedine (**8**) and spectral evidence.

Chemical investigations conducted on the seeds of the fruit of the tree *Casimiroa edulis* La Llave et Lejarza have shown them to contain a variety of constituents.[2-4] The principal constituent, the alkaloid casimiroedine (**7**), was found to be the cinnamic acid amide of casimidine (**6**).[5] Degradation studies[6] on casimidine confirmed the presence of *N*-methylhistamine and a carbohydrate fragment. An X-ray analysis[7,8] firmly established the structure of the carbohydrate as β-D-glucose and of casimidine as 4-[2-(methylamino)-ethyl]-1-(β-D-glucopyranosyl)imidazole. These studies provided the basic structure of casimiroedine (**7**) and left one question unanswered, whether casimiroedine was the *cis*- or *trans*-cinnamic acid amide of **6**. This final question has now been resolved by the total synthesis of casimiroedine.[1b]

Results and Discussion

Chemical Synthesis. The chloromercury derivative[9] (**2**) of 4-(2-chloroethyl)imidazole hydrochloride[10,11] (**1**) (Scheme I) was glycosylated with 2,3,4,6-tetra-*O*-acetyl-α-D-glucosyl bromide[12] (**3**) to provide **4** as a thick syrup. Rather than isolate nucleoside material at this point, the syrup was treated with methanolic methylamine in a steel reaction vessel at 100°. The purpose of this step was twofold: deacetylation of the glucose moiety and nucleophilic displacement of the chloro group. After removal of the excess methanolic methylamine, the

Scheme I



syrup (**5**) was purified on a Dowex 50W-X2 (NH_4^+) resin column which provided a single product (tlc). This crystalline solid was tentatively identified on the basis of pmr spectroscopy and elemental analysis as 4-[2-(methylamino)ethyl]-1-(β-D-glucopyranosyl)imidazole (**6**, casimidine). This assignment was confirmed by a comparison of the ir and mass spectra (EI) of this

(1) (a) This investigation was supported in part by Research Contract No. C72-3710 with the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Public Health Service. (b) R. P. Panzica and L. B. Townsend, presented in part before the Organic Chemistry Division, 24th Annual Northwest Regional Meeting of the American Chemical Society, University of Utah, Salt Lake City, Utah, June 1969, No. 149.

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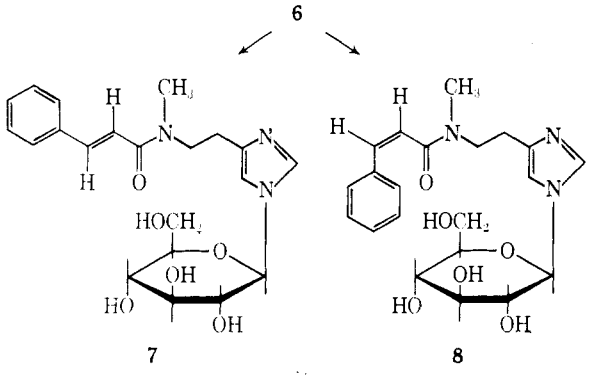
nucleoside with the ir and mass spectra of an authentic sample of casimidine.[13]

This preparation of casimidine (**6**) provided one of the essential precursors for the total synthesis of casimiroedine (**7**). However, before we attempted to synthesize **7**, several key decisions were required, *e.g.*, a cinnamoyl derivative having the correct stereochemistry had to be selected and the form of this derivative had to be suitable for peptide formation. The route we had envisaged for the synthesis of **7** required coupling of the cinnamoyl derivative directly with casimidine. On this basis, we eliminated the acid chloride method, since it would entail protection of the hydroxyl groups on the glucosyl moiety and necessitate two additional steps, *i.e.*, blocking and deblocking. This decision narrowed our choice to the use of *cis*- and *trans*-cinnamic acids as the functional form of the cinnamoyl precursor.

At the onset of our synthesis of casimiroedine[1b] only a limited amount of peptide synthesis had been conducted in the area of nucleosides.[14,15] This work[14] dealt mainly with the use of dicyclohexylcarbodiimide (DCC) as the coupling reagent. DCC has been used extensively in the formation of peptide linkages in the syntheses of nucleoside peptides. It has also been used to form ester bonds between amino acids and the free hydroxyl groups of the carbohydrate moiety.[16] For reasons similar to those discussed for the acid chloride method (*vide supra*), we decided against the use of DCC as a coupling agent. This prompted us to examine the use of a new coupling reagent, EEDQ (*N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline). This reagent has been shown[17] to effect peptide coupling in good yield with a minimum of side reactions (Scheme II).

Scheme II



When casimidine (**6**) was reacted with *trans*-cinnamic acid in the presence of EEDQ, only one nucleoside product was obtained (tlc) in 70% yield. The pmr (60 MHz) spectra of this new nucleoside revealed that chemical coupling had occurred only between the methylamino group of **6** and the carboxylic function of *trans*-cinnamic acid. A comparison of the ir, uv, and mass spectra (EI) of this nucleoside with those from an authentic sample of casimiroedine[13] showed them to be identical and established that casimiroedine (**7**) was the *trans*-cinnamamide of casimidine (**6**). For further corroboration of this assignment, we have synthesized the cis analog (**8**) from *cis*-cinnamic acid[18] and **6** using the same reaction conditions which were established for the synthesis of **7**.

Stereochemistry. The chemical proof for the assignment of configuration of the cinnamoyl moiety was aided by the synthesis of *cis*-casimiroedine (**8**). This isomer (**8**) proved to be even more valuable in the interpretation of the spectral data. Without the spectral information provided by the cis isomer (**8**), the task of assigning (and confirming) the trans configuration to **7** would have been extremely difficult.

In making our assignment of stereochemistry, we placed our major emphasis on pmr spectroscopy. The pmr spectrum (60 MHz, DMSO-d_6) of **7** was not as straightforward as we had hoped. The "AB quartet" of the ethylenic protons was definitely overlapped with those protons from the benzene and imidazole rings. In order to confirm our suspicion that this occurrence was primarily a result of the shielding contribution of the solvent,[19] we examined the spectra of a model compound, *N*,*N*-dimethyl-*trans*-cinnamamide, in several solvents. As the solvent was changed from $CDCl_3$ to DMSO-d_6 (Table II), a significant decrease in the chemical shift ($\Delta\nu_{AB}$) of the ethylenic protons was observed, as well as an increase in the magnetic nonequivalence of the *N*-methyl groups. Whether this effect was caused by the increase in polarizability of the solvent[19,20] in going from $CDCl_3$ to DMSO-d_6, or a change in orientation, *i.e.*, restriction in rotation due to an increase in hydrogen bonding, thus increasing the population of a certain rotomer and increasing the degree of C–N double bond character,[19,21] was not completely explored since our main objective was to obtain a simple spectrum such that the J_{trans} coupling constant could be measured. Unfortunately, we were limited to the use of DMSO-d_6 as solvent, since **7** was found to be insoluble in most other deuterated organic solvents. Therefore, to avoid the possibility of having to interpret a complex spectrum, we obtained 220 MHz spectra[22] for both the cis and trans isomers. For the trans isomer (**7**), the higher frequency spectrum failed to resolve the apparent problem. The J_{trans} coupling constant could not be determined because of the still existing overlap with aromatic protons. However, the pmr spectra obtained for **8** (Figure 1) were now very easy to

(13) The authors wish to thank Professor Carl Djerassi for his generous gift of the authentic samples of casimidine and casimiroedine.

(14) E. Schroder and K. Lubke, "The Peptides," Academic Press, New York, N. Y., 1965, p 305.

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(22) The authors wish to thank: Dr. L. Herr and Prof. G. D. Daves, Jr., Oregon Graduate Center, for the 100-MHz spectra (Varian HA-100) of **7**; J. C. Smith, University of Utah, for the 100-MHz spectra (Varian XL-100-12) of **8**; and Dr. D. H. Live and Prof. S. I. Chan, California Institute of Technology, for the 220-MHz spectra (Varian HR-220) of **7** and **8**.

interpret. The aromatic protons of the imidazole ring could be assigned and the *cis*-ethylenic quartet was found to closely approximate a simple first-order AX system ($\Delta\nu_{AB}$ = 63.75, $\Delta\nu/J$ = 5). We were able to determine the J_{AB} coupling constant, which was found to be 13 Hz (cis). In conjunction with the J_{trans} coupling constant data determined for *N,N*-dimethyl-*trans*-cinnamamide and that reported for the *cis*- and *trans*-cinnamic acids,[19] our data definitely confirmed our chemical proof that casimiroedine (7) was the trans isomer.

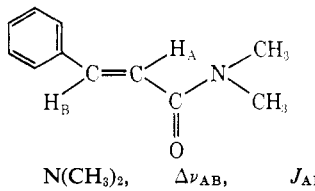
Conclusion. The composite of our chemical and physical evidence has shown the imidazole alkaloid casimiroedine (7) to be the *trans*-cinnamamide of casimidine (6). It is noteworthy that, although casimiroedine has been shown not to be one of the constituents which causes adverse physiological properties[2,4] when the seeds of the "Zapote blanco" ("white fruit") are ingested, it has been shown to possess activity (anticancer) against lymphoid leukemia L-1210.[23]

Table I. Ultraviolet Absorption Data for Casimiroedine and *cis*-Casimiroedine

No.	Compound	pH	λ_{max}, nm	$\epsilon_{max} \times 10^{-3}$	λ_{min}, nm	$\epsilon_{min} \times 10^{-3}$
7	Casimiroedine	1	283	20.25	240	6.19
			223.5 sh[a]	15.61		
			218	18.19		
		11	282	19.98	235	7.70
			224.5 sh	12.19		
		EtOH	281	20.63	234.5	4.64
			223.5 sh	15.13		
			218.5	17.95		
	Casimiroedine[b]	EtOH	280[c]	20.00		
			219[c]	18.20		
			281[d]	21.50		
			218[d]	20.00		
8	*cis*-Casimiroedine	1	261	9.17	235	5.92
		11	249	15.80	222	6.67
		EtOH	256	12.72	232	9.21

[a] sh = shoulder. [b] Authentic sample. [c] Reference 5. [d] Reference 4.

Table II. Chemical Shift (Hz) of the Vinylic Protons and Magnetic Nonequivalence (Hz) of the *N*-Methyl Groups in *N,N*-Dimethyl-*trans*-cinnamamide[a] as a Function of Solvent[b]



Solvent[c,d]	$N(CH_3)_2$, Hz	$\Delta\nu_{AB}$, Hz	J_{AB}, Hz	$\Delta\nu/J$
$CDCl_3$	0	47.2	15.6	3.0
Acetonitrile-d_3	8.75	28.2	15.8	1.8
Acetone-d_6	10.00	24.2	16.0	1.5
DMSO-d_6	12.75		16.0[e]	

[a] H. Staudinger and N. Kon, *Justus Liebigs Ann. Chem*, **384**, 38 (1911). [b] Spectra obtained on a Varian A 56/60 MHz spectrometer. [c] Concentration was 40 mg/0.4 ml of solvent. [d] The internal standard for $CDCl_3$, acetonitrile-d_3, and acetone-d_6 was TMS. The internal standard for DMSO-d_6 was DSS. [e] Only the upfield portion of the AB quartet was discernible.

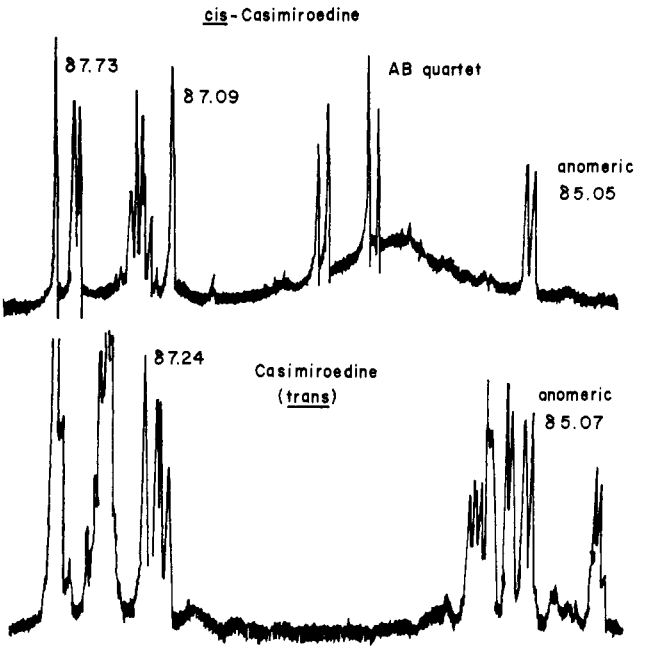


Figure 1. 220 MHz spectra of *cis*-casimiroedine and casimiroedine (δ 8.0–4.0, DMSO-d_6).

Table III. R_f Values of *cis*- and *trans*-Casimiroedine[a,b]

No.	Compound	Chromatographic solvent systems[c] 1	2	3	4	5
7	Casimiroedine	0.76	0.43	0.75	0.32	0.81
	Casimiroedine[d]	0.76	0.43	0.75	0.33	0.81
8	*cis*-Casimiroedine	0.75	0.64	0.92	0.70	0.80

[a] All compounds were run on Whatman No. 1 chromatographic paper and the descending technique was used. [b] Short-wave ultraviolet light (254 nm) was used to detect spots. [c] Chromatographic solvent systems: 1, ethanol–water, 7:3 (v/v); 2, 1-butanol saturated with water; 3, 5% aqueous ammonium bicarbonate (w/w); 4, ethyl acetate–1-propanol–water, 4:1:2 (v/v) upper phase; 5, 1-propanol–ammonium hydroxide (sp gravity 0.90)–water, 6:3:1 (v/v). [d] Authentic sample.

Experimental Section

Melting points were determined with a Thomas Hoover melting point apparatus and are uncorrected. The infrared spectra were determined in pressed potassium bromide disks with a Beckman IR-8 spectrometer and the ultraviolet absorption spectra were recorded on a Beckman DK-2 spectrometer. The chemical ionization (CI) mass spectra were obtained on a Varian CH7 instrument, modified for high pressure operation,[24] using methane (CH_4) reagent gas, accelerating potential 2 kV, ionizing electron energy 2.5 kV, repeller voltage 0.00 V, and reagent gas pressure, 0.5 Torr. All samples (1–10 μg) were introduced by direct probe. The electron ionization (EI) mass spectra were recorded on a Perkin-Elmer 270 instrument, ionizing energy, 70 eV. All samples were introduced by direct probe. The optical rotations were measured with a Perkin-Elmer Model 141 automatic digital readout polarimeter. Thin-layer chromatography (tlc) was run on glass plates coated (250 μm) with SilicAR 7 GF (Mallinckrodt). Elemental analyses were performed by Heterocyclic Chemical Corp., Harrisonville, Mo.

4-[2-(Methylamino)ethyl]-1-(β-D-glucopyranosyl)imidazole (6, Casimidine). 4-(2-Chloroethyl)imidazole hydrochloride[10,11] (**1**) (6.46 g, 37.6 mmol) and sodium carbonate (4.00 g, 37.6 mmol) were dissolved in hot distilled water (300 ml) followed by the addition of

(23) Preliminary results obtained for casimiroedine against lymphoid leukemia L-1210 are as follows: host, BDF_1; dose mg/kg, 200 mg; survivors, 6/6; animal weight difference (T − C), −2.0; tumor evaluation (T/C), 13.2/9.5; %, 138; test status, 22. The evaluation of the activity is in accordance with the criteria of the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health.

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9.7 g of analytical Celite. A hot mercuric chloride (10.25 g, 37.6 mmol) solution (300 ml) was added dropwise to this stirred suspension. The resulting cream-brown precipitate was collected by filtration, washed with water (2 × 100 ml), and then dried *in vacuo* for 2.5 hr at 70°. The finely powdered chloromercury salt (**2**)[9] was suspended in xylene (400 ml) in a 1-l. three-necked round-bottomed flask and azeotropically dried by employing a Dean–Stark trap. To the suspension was added tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**3**)[12] (16.5 g, 40.1 mmol) which had been previously dissolved in hot xylene (200 ml). The reaction mixture was heated at reflux temperature and mechanically stirred for 3 hr and then filtered through a Celite pad (2.5 × 11 cm). The Celite pad was then crushed and washed with hot toluene (2 × 100 ml) and warm methylene chloride (5 × 100 ml). The combined wash and xylene filtrate were evaporated *in vacuo* to a syrup. The syrup was then dissolved in methylene chloride (400 ml). The methylene chloride solution was extracted with a 30% potassium iodide solution (3 × 100 ml), dried over anhydrous magnesium sulfate, and evaporated *in vacuo* to a light-brown syrup (**4**). The syrup (**4**) was dissolved in methanol (80 g) containing monomethylamine (40 g) and the solution was heated in a steel reaction vessel for 15 hr at 100°. The excess methanol and monomethylamine were removed *in vacuo* (water bath 40°) and the resulting syrup (**5**) was dissolved in a minimum amount of water and applied to a pretreated column[25] (3 × 35 cm) of Dowex 50 W-X2 (NH_4^+, 200–400 mesh). The column was eluted with water (500 ml), and gradient eluted with 1 $N \rightarrow 2$ N ammonium hydroxide (500 ml) and then by 1.5 l. of 2 N ammonium hydroxide. Fractions of 100 ml were collected, and fractions 10–15 were pooled and evaporated *in vacuo* to furnish 3.65 g (33% overall) of casimidine as a white foam. Recrystallization from methanol provided **6** as colorless beads: mp 207–209° (no change on taking mixture melting point with authentic sample); $[\alpha]^{27}D$ +7.00 (*c* 1.00, 80% ethanol) [lit.[5] mp 207–209°, $[\alpha]D$ +11.00 (80% ethanol)]; pmr (DMSO-d_6) δ 2.33 (s, 3, NCH_3), 4.41 (br s, 5, OH, NH), 5.06 (d, 1, $J_{1',2'}$ = 8.0 Hz, 1′ H), 7.07 (s, 1, 5 H), 7.73 (s, 1, 2 H); mass spectrum (CI, 170°) M + H (mass/rel intensity) (288/100), M + C_2H_5 (316/12), M + C_3H_5 (328/4), M − CH_2O (257/2), M − C_2H_3N (244/4), b + 2 H (126/16), b + CH_2O (154/5).

Anal. Calcd for $C_{12}H_{21}N_3O_5$: C, 50.16; H, 7.37; N, 14.63. Found: C, 50.32; H, 7.34; N, 14.89.

4-[2-(*N*-Methyl-*N*-*trans*-cinnamoylamino)ethyl]-1-(β-D-glucopyranosyl)imidazole (7, Casimiroedine). *trans*-Cinnamic acid (154 mg, 1.04 mmol), *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) (258 mg, 1.08 mmol), and dry benzene (40 ml) were added to a solution of casimidine (**6**) (300 mg, 1.04 mmol) in anhydrous methanol (15 ml). The reaction mixture was stirred at room temperature for 20 hr and, after evaporation of the solvent, the residue was crystallized from ethanol to give 304 mg (70%) of casimiroedine. An analytical sample was crystallized from ethanol to give colorless beads: mp 223–224° (no change on taking mixture melting point with authentic sample); $[\alpha]^{27}D$ −30.7 (*c* 1.00, 1% hydrochloric acid) [lit.[5] mp 223–224°, $[\alpha]D$ −27 (1% hydrochloric acid)]; pmr (DMSO-d_6) δ 2.48 (s, 3, NCH_3), 5.06 (d, 1, $J_{1',2'}$ = 8.75 Hz, 1′H); mass spectrum[26] (CI, 200°) M + H (418/100), M + C_2H_5 (446/19), M + C_3H_5 (458/11), b + 2 H (256/32), M + H (288/25; from **6**), M − CH_2O (257/25; from **6**).

Anal. Calcd for $C_{21}H_{27}N_3O_6$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.65; H, 6.72; N, 10.38.

4-[2-(*N*-Methyl-*N*-*cis*-cinnamoylamino)ethyl]-1-(β-D-glucopyranosyl)imidazole 8, *cis*-Casimiroedine). Experimental conditions similar to those used for the preparation of **7** were used for the preparation of **8** except that *trans*-cinnamic acid was replaced by *cis*-cinnamic acid. After the reaction solution had been stirred for 4 hr, the crystalline precipitate which had formed was collected by filtration. The filtrate was stirred for an additional 16 hr and the small amount of precipitate which had formed was again collected by filtration. The fluffy needles were recrystallized from ethanol to give 163 mg (37%) of **8**: mp 187–189°; $[\alpha]^{27}D$ +10.65 (*c* 1.00, 1% hydrochloric acid); pmr (DMSO-d_6) δ 2.47 (s, 3, NCH_3), 5.05 (d, 1, $J_{1',2'}$ = 8.75 Hz, 1′ H), 5.95, 6.23 (AB q, 2, J_{AB} = 13 Hz), 7.09 (s, 1, 5 H) 7.73 (s, 1, 2 H).

Anal. Calcd for $C_{21}H_{27}N_3O_6$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.28; H, 6.56; N, 10.38.

Acknowledgment. The authors wish to thank Dr. Robert J. Rousseau for useful suggestions throughout this investigation.

(25) The column was purged with concentrated ammonium hydroxide and then washed with distilled water until neutral.

(26) A peak at M − 57 (360/62) was observed in the CI mass spectrum of 7. This ion may result from a cyclization of the cinnamoyl group[27] with the imidazole moiety followed by elimination of a C_3H_7N fragment. The CI mass spectra of *cis*-casimiroedine (**8**) also revealed some unusual characteristics. *cis*-Casimiroedine, as well as the trifluoroacetyl[28] and trimethylsilyl[28] derivatives, failed to produce a protonated molecular ion. In fact, the spectrum (190°) of **8** was extremely similar to that of casimidine (**6**); major fragments were 288 (M + H), 316 (M + C_2H_5), 328 (M + C_3H_5), 126 (b + 2H), 154 (b + CH_2O), 257 (M − CH_2O), 244 (M − C_2H_5N). This mass spectral behavior observed for **8** may be a means for distinguishing between *cis*- and *trans*-cinnamides representative of the systems presented. A thorough study of the above spectral features is now being investigated in our laboratories.

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(28) The authors wish to thank Dr. James A. McCloskey and his colleagues (Institute for Lipid Research, Baylor College of Medicine) for the CI mass spectra on these derivatives.