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Synthesis of *endo*- and *exo*-5-[4(5)-Imidazolyl]bicyclo[2.2.1]hept-*endo*-2-yl *trans*-Cinnamates

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The synthesis and separation of *endo*- and *exo*-5-[4(5)-imidazolyl]bicyclo[2.2.1]hept-*endo*-2-yl *trans*-cinnamates *via* 5-(1-keto-2-hydroxyethyl)bicyclo[2.2.1]hept-2-enes are described. The imidazolyl derivatives have a rigid bicyclo[2.2.1]heptane structure; the endo compound was synthesized as a model for α-chymotrypsin and the exo compound was synthesized for purposes of comparison. The mode of 2,5 disubstitution of bicyclo[2.2.1]heptane was determined by a double resonance experiment using nmr.

Enzyme model studies are becoming increasingly important because of interest in enzyme mechanism and the design of synthetic catalysts with enzyme-like activity. However, a difficult problem has been the synthesis of model compounds that can mimic enzyme structure or mechanism, or both. The X-ray structure of α-chymotrypsin has been determined, indicating the spatial alignment of the important functionalities at the active site.[2] Enzyme mechanistic studies have clarified the roles of the functional groups, especially those of the histidine imidazolyl and serine hydroxyl groups in terms of organic reaction mechanisms.[3] Therefore, α-chymotrypsin could be the first enzyme whose catalytic efficiency can be approximated by a synthetic model.

We have approached the synthesis of an enzyme model which has a rigid structure with the correct spatial alignment of the imidazolyl and hydroxyl groups as in α-chymotrypsin (approximately 3 nm from one another). For this purpose we have chosen the bicyclo[2.2.1]heptane ring system as the framework that bears the two functional groups, because its internal free rotations are frozen and its endo-2-, endo-5-disubstituted structure assumes the alignment indicated above. With chymotrypsin, the reaction proceeds in two steps: an acylation of the enzyme on the serine hydroxyl group and a deacylation of the acyl enzyme, an ester.

In this report we describe the synthesis of the titled model compounds which simulate an acyl enzyme in the correct (endo) and incorrect (exo) stereochemistries. In another paper we will report their catalytic effectiveness. *trans*-Cinnamates were used because they are more readily available and have been used before.[3] The endo compound, as expected, was considerably faster than the exo compound, although the former does not have the reactivity of the cinnamoyl enzyme.

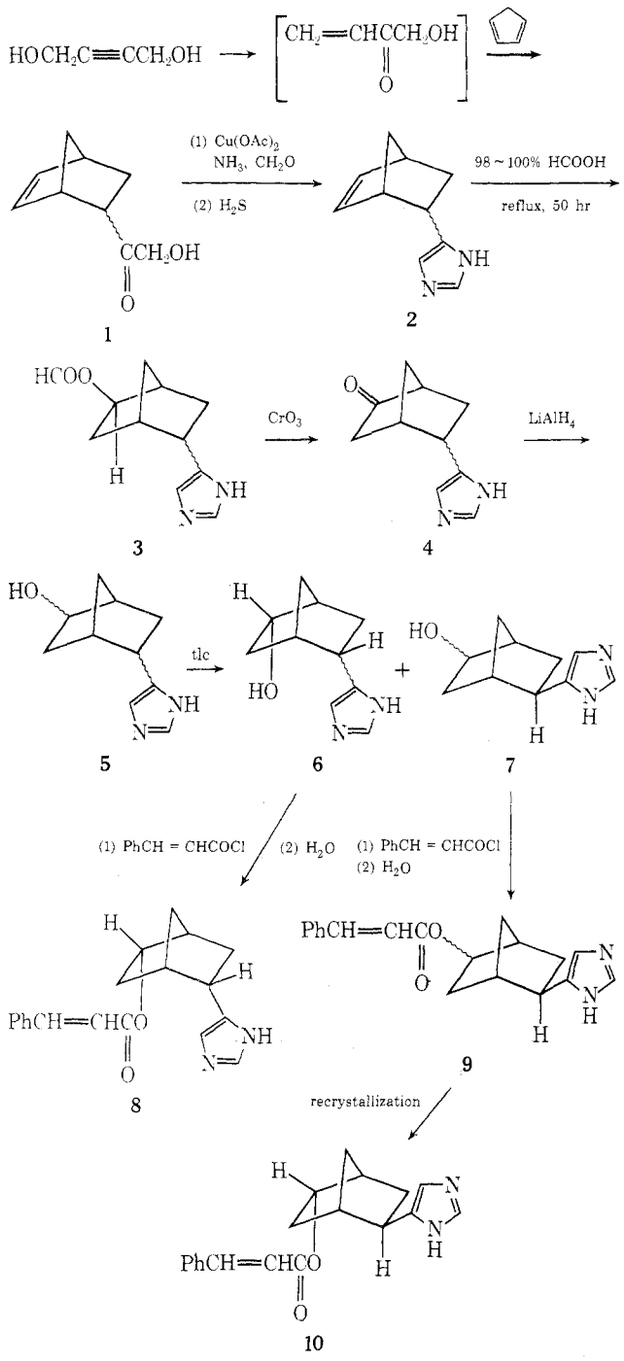
Results and Discussion

Hitherto, only one report concerning cyclic imidazole derivatives has appeared, namely the synthesis of 2- and 3-keto-*endo*-5-(2-imidazolyl)bicyclo[2.2.2]octane.[4a] The synthetic method used for this compound, however, cannot be applied to the present enzyme model, because it does not afford 4(5)-imidazolyl derivatives.

Our synthetic route is shown in Scheme I. At an early stage of this work, the methyl ketone was more easily available and stable than the corresponding hydroxymethyl ketone **1** and was tried as a precursor for the imidazole derivative **2**. But oxidation with selenium dioxide failed to give the glyoxal, which could be converted to **2**. The intermediate hydroxymethyl vinyl ketone is so easily polymerizable[4b] that it was allowed to react with cyclopentadiene without distillation from the reaction mixture, giving the crude Diels–Alder adduct **1** in 18% yield. Since this yield was nearly that reported by Reppe and coworkers for the hydroxymethyl ketone from 2-butyne-1,4-diol,[4b] the Diels–Alder reaction probably proceeded almost quantitatively.

For the determination of the endo:exo ratio, ketone **1** was fractionally distilled through a spinning band column, giving fractions of nearly 100% endo ketone and 85% exo ketone. The nmr spectrum of the endo ketone was consistent with that of methyl *endo*-2-norbornyl ketone.[5] In the spectrum of the exo ketone, a signal with four main peaks appeared at higher field than that of the exo C-5 proton ($\Delta\delta$ = 0.6) and was assigned to the endo C-5 proton.[5] Another important change was seen in the pattern of the olefinic protons. In the endo ketone they appeared as two symmetrical doublets centered at δ 6.16 and 5.81, but in the exo ketone the signal at higher field was diminished and was seen at lower field. Since this difference was adequate for quantitative treatment, this was used for determination of the

Scheme I



endo:exo ratio of the ketone. Separation of the endo and exo ketones on a preparative scale was not preferable at this stage, because endo–exo isomerization took place in subsequent reactions.

Imidazole formation was achieved in good yield (60–70%) according to the method of Weidenhagen.[6] However, this reaction was found to be accompanied by endo–exo isomerization.

When 10 g of the 100% endo ketone was heated to 70–80° with cupric acetate, ammonia water, and formalin, the slightly green cuprous salt began to precipitate in 3 min and after 10 min it was collected by filtration. The filtrate was heated again for 1 hr, and the precipitate was collected. As Table I shows, it is probable that there exists a base-catalyzed equilibration between the endo and exo ketones in basic solution since the longer the ketone is in contact with

Table I
Endo:Exo Ratios of *endo*- and *exo*-[4(5)Imidazolyl]bicyclo[2.2.1]hept-2-enes

Starting ketone	Time, min	Endo:Exo 2
100% endo	10	93:7
100% endo	60	82:18
85% exo	60	26:74
77:23 mixture of endo and exo	60	75:25

the basic solution, the higher the exo content of the imidazole derivative.

The endo:exo ratios of the imidazole derivative **2** were determined by the same method that was used for the ketone **1**, since the signals of the olefinic protons in the nmr spectra of **2** were very similar to those of the ketone.

The imidazole ring C-4(5) proton of **2** was assigned to two somewhat broad singlets at δ 6.83 and 6.63. The former corresponded to the *endo*-imidazole derivative in conjunction with the signal of the exo C-5 proton at δ 3.37 and the latter to the *exo*-imidazole derivative, which had the endo C-5 proton at δ 2.68. The imidazole ring C-2 proton appeared at δ 7.53 and 7.58, corresponding to the endo and exo isomers, respectively. The difference in this case ($\Delta\delta$ = 0.05) was quite small compared with that of the C-4(5) proton ($\Delta\delta$ = 0.20).

Purification of the imidazole derivative **2** proved difficult. Crystallization from hot water or as the picrate or hydrochloride failed to give crystals. Thin layer chromatography using basic alumina or silica gel did not remove the impurity.

After these trials, the number of the olefinic protons relative to the others was found to decrease as indicated by nmr, suggesting the occurrence of polymerization. Therefore, the crude imidazole derivative **2** was used for the next step.

Introduction of a functional group which could be converted to an *endo*-hydroxyl group at the 2 or 3 position of the bicyclic skeleton was tried in various ways. Hydroboration and oxymercuration were unworkable. Palladium chloride oxidation[4a] gave the corresponding ketone in poor yield and thus was unfavorable for synthetic purposes. However, 98–100% formic acid proved excellent. By refluxing in excess formic acid for 50–55 hr, the unsaturated imidazole derivative **2** was converted to the corresponding formate **3** in 80–90% yield, although it required longer reaction time than the 2–3 hr in the case of norbornene.[7] During this reaction period, endo–exo isomerization of the imidazolyl group occurred, a 75:25 mixture of the *endo*- and *exo*-imidazoles **2** being changed to a 60–70:40–30 mixture of the *endo*- and *exo*-imidazoles **3**. The formoxy group was exclusively exo. This stereochemistry was determined by nmr using the signals of the protons attached at the imidazolyl and formoxy carbons. It was not possible to determine whether the formoxy group was introduced at C-2 or C-3 from nmr. But the rather sharp singlet of the formyl proton at δ 7.97 suggested that the group was introduced only at either of the two carbons. The location of the formoxy group at C-2 was firmly deduced from compound **8**.

Oxidation of the crude formic ester **3** to the corresponding ketone **4** was achieved by using chromic acid in aqueous acetone.[7] The use of acetone as a solvent component has the two advantages of high yield (70–80%) and easy separation of the product from the reaction mixture. Ketone **4** has a strong absorption band at 1740 cm^{-1} characteristic for bicyclo[2.2.1]heptan-2-one[8] and was identified by means of

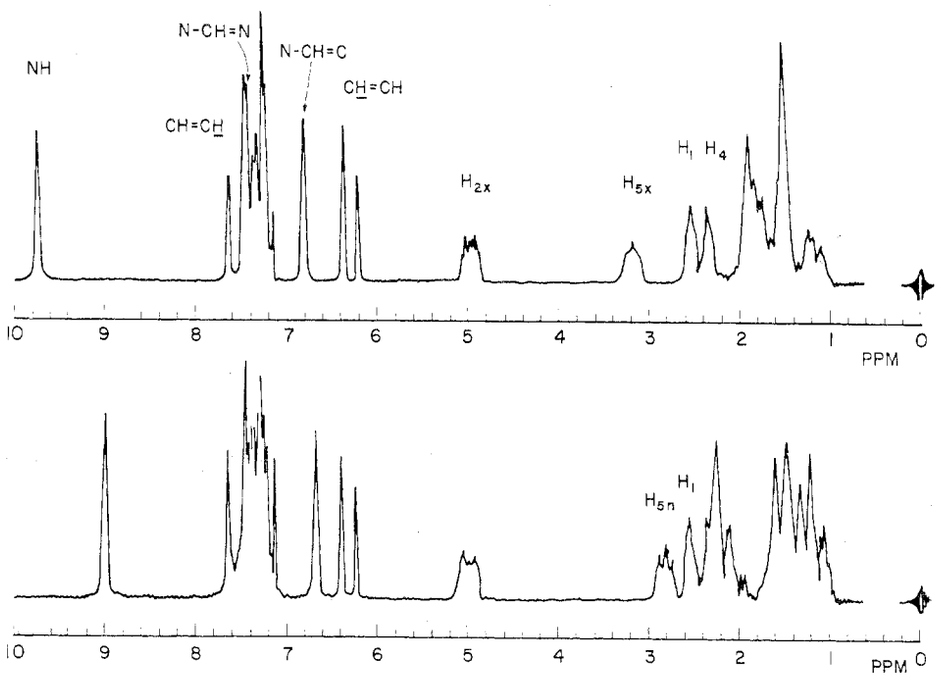


Figure 1. Nmr spectra of *endo*-5-[4(5)-imidazolyl]bicyclo[2.2.1]hept-*endo*-2-yl *trans*-cinnamate (**8**) (upper) and *exo*-5-[4(5)-imidazolyl]bicyclo[2.2.1]hept-endo-2-yl *trans*-cinnamate (**10**) (lower). In $CDCl_3$ at 100 MHz, hexamethyldisiloxane as internal standard.

ir, nmr, and mass spectra. Furthermore, ketone **4** was converted to the corresponding 2,4-dinitrophenylhydrazone and identified after recrystallization.

Ketone **4** was a slightly yellow, transparent, and viscous semisolid; its crystallization was not successful. Purification by thin layer chromatography failed. Integration of the C-5 exo proton at δ 3.45 in the nmr spectrum showed that it was a 60–70:40–30 mixture of the endo and exo imidazoles, the endo:exo ratio not having changed from that of the preceding formate **3**. Another important feature of the spectrum was the appearance of the imidazole C-4(5) proton as two singlets ($\Delta\delta$ = 0.03), which seemed to correspond to the endo and exo isomers, although the imidazole C-2 proton appeared as a somewhat broad singlet. The same feature was found in the nmr spectrum of its purified 2,4-dinitrophenylhydrazone derivative.

Reduction of the crude ketone **4** with lithium aluminum hydride in tetrahydrofuran gave the corresponding crude alcohol **5** in 80–90% yield. The endo:exo ratio of the resulting hydroxyl group, which was determined by nmr using the signals of the proton attached to the alcoholic carbon, was found to be about 9:1, similar to that for the hydride reduction product of 2-norbornanone.[9] Lithium trimethoxyaluminum hydride as the reductant gave almost the same endo:exo ratio as above, in sharp contrast to the 98% endo selectivity in the case of 2-norbornanone.[9,10] The endo:exo ratio of the imidazolyl group was found to be lowered to 50:50, indicating endo–exo isomerization during reduction.

Thin layer chromatography using basic alumina proved effective for isolation of *endo*-5[4(5)-imidazolyl]bicyclo-[2.2.1]heptan-*endo*-2-ol (**6**) from the stereoisomeric mixture **5**. The alcohol **6** has a larger R_f value (0.46) than other isomers (0.24); in other words, it traveled further on a thin layer plate. This is quite reasonable because its two functional groups can interact intramolecularly or sterically hinder one another against adsorptive interaction with the basic alumina. Both the imidazolyl and hydroxyl groups were nearly 100% endo as determined by the signals of the protons attached to the carbons which bear those groups. A sharp singlet of the C-4(5) proton of the imidazolyl group, $\Delta\delta$ for the endo and exo isomers being 0.10, was consistent with **6**. Compound **6** was very hygroscopic. When it was dried *in vacuo*, it hardened to an amorphous solid including traces of moisture and methanol.

The fraction of R_f 0.24, from its nmr spectrum, consisted of a compound containing the *exo*-imidazolyl group, with a trace of the endo group with the *endo*- and *exo*-hydroxyl groups in a ratio of 4:1. Thus, the main component in this fraction was probably *exo*-5-[4(5)-imidazolyl]bicyclo-[2.2.1]heptan-*endo*-2-ol, which was isolated later as the *trans*-cinnamate **10** after recrystallization.

O-Acylated compound **8** was obtained from **6** *via* the *O*- and *N*-diacylated intermediate, which was formed in the reaction of **6** with *trans*-cinnamoyl chloride in chloroform. The use of chloroform as solvent is quite important because it completely dissolves the imidazolium hydrochloride generated in the reaction and ensures a homogeneous product. The *O*- and *N*-diacylated intermediate was dissolved in a mixed solvent of chloroform–methanol–water, then partially hydrolyzed, and crystallized to give **8**. Isolation of **8** from the mixture of O-acylated imidazoles derived from **5** was not successful by thin layer chromatography. Compound **10** was obtained from **7** using the same reactions as **8**. However, it required purification by column chromatography and then by fractional crystallization.

Both compounds **8** and **10** were stable, white crystalline materials. The former melts at 130–132° which is 44° lower than the latter, indicating weaker intermolecular interaction in the former as anticipated by its endo,endo orientation.

Significant differences were not found in the ir spectra of **8** and **10**. The nmr spectra of these compounds, however, gave valuable information about their structures. The spectra obtained at 100 MHz are shown in Figure 1. These spectra clearly indicate the endo or exo orientation of each functional group. The chemical shifts of the protons attached to the acyloxy-bearing carbons are in good agreement with literature values.[5] The carbocyclic part of the spectrum of **6** or **8** is very similar to that of *endo*-2-norbornanol or its acetate, except for the existence of the signals due to the *endo*-imidazolyl group.

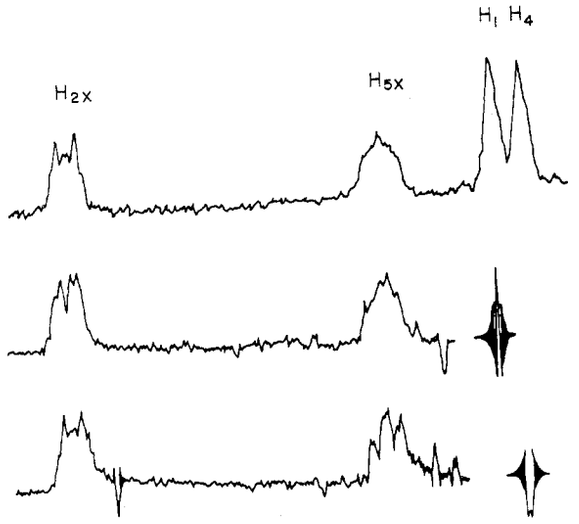


Figure 2. A double resonance experiment for *endo*-5-[4(5)-imidazolyl]bicyclo[2.2.1]hept-*endo*-2-yl *trans*-cinnamate (**8**). In $CDCl_3$ at 100 MHz.

The question of 2,5 or 2,6 disubstitution was answered definitively by a double resonance experiment at 100 MHz. The spectrum is shown in Figure 2, indicating that H_1 couples with H_{2x} but not with H_{5x}, and H_4 couples with H_{5x} but not with H_{2x}. This result indicates unequivocally 2,5 disubstitution. Since only one mode of disubstitution was observed in the intermediates **3** and **4**, the addition of formic acid to **2** must have been regiospecific, giving only the 2,5-disubstituted bicyclo[2.2.1]heptane.

Experimental Section

All melting points and boiling points are uncorrected. Nmr spectra were obtained on a Hitachi Model R-24 spectrometer (60 MHz). In $CDCl_3$ solutions, TMS was used as internal standard; in DMSO-d_6 or CD_3OD solutions the solvent signal at δ 2.50 or 3.35, respectively, was used as internal standard. A double resonance experiment was carried out on a Varian HA-100 spectrometer. Mass spectra were obtained on a Hitachi RMS-4 spectrometer (70 eV). Elemental analyses were carried out by Mr. Ei-ichiro Amano at Okayama University.

***endo*- and *exo*-5-(1-Keto-2-hydroxyethyl)bicyclo[2.2.1]-hept-2-enes (1).** According to the procedure of Reppe and coworkers,[4b] 100 g (1.16 mol) of 2-butyne-1,4-diol was isomerized to hydroxymethyl vinyl ketone in 500 ml of reagent grade ethyl acetate with mercuric oxide (red), boron trifluoride etherate, and trichloroacetic acid as catalysts. After isomerization, the clear yellow solution was decanted, washed with a dilute aqueous sodium carbonate solution, and evaporated *in vacuo*. To the resulting viscous, orange liquid, 30 g (0.45 mol) of freshly distilled cyclopentadiene was added with stirring. Vigorous heat evolution was observed within a few minutes and the reaction mixture was cooled in an ice bath so that the temperature did not exceed 40°. Heat evolution continued for about 10 min. The solution was allowed to stand overnight at room temperature and then distilled *in vacuo*, yielding 31 g (18%) of the crude product. This was fractionally distilled through a spinning band column (6 mm × 60 cm, 30 plates), giving 2.1 g of a 30:70 mixture, bp 85–88° (8.5 mm), and 12 g of a 71:29 mixture, bp 91–92° (8.5 mm), of the endo and exo ketones **1**, and 3.5 g, bp 92° (8.5 mm), of the endo (>98%) ketone **1**. About 10 g of a liquid that solidified remained in the still pot. The second and third fractions were combined, giving 15.5 g of a 77:23 mixture of the endo and exo ketones **1** for further use: ir (neat) 3430 (OH), 3060 (=C—H), 1710 (C=O), 1570 (C=C), 1080 cm^{-1} (C–O).

Nmr (endo > 98%) ($CDCl_3$) δ 6.16 (1 H, dd, J = 3 and 6 Hz, C**H**=CH), 5.81 (1 H, dd, J = 3 and 6 Hz, CH=C**H**), 4.22 (2 H, s, CH_2O), 3.22 (1 H, s, OH), 3.19 (1 H, m, H_4), 2.96 (3 H, m, H_1 and H_{5x}). Nmr (exo 85%, endo 15%[11] $CDCl_3$) δ 6.15 (1.85 H, m, *exo*-c**H**=C**H** and *endo*-C**H**=CH), 5.83 (0.15 H, dd, J = 3 and 6 Hz, *endo*-CH=C**H**), 4.33 (s, *exo*-CH_2O), 4.25 (s, *endo*-CH_2O), 3.22 (1 H, s, OH), 2.95 (*ca.* 2 H, m, H_1, H_4, and H_{5x}), 2.35 (*ca.* 1 H, m, H_{5n}).

***endo*- and *exo*-5-[4(5)-Imidazolyl]bicyclo[2.2.1]hept-2-enes (2).** In 150 ml of ethanol 15.5 g (0.103 mol) of the mixed ketones **1** was dissolved and then diluted with 80 ml of warm water. To this warm solution were added 42 g (0.21 mol) of cupric acetate monohydrate in 180 ml (2.5 mol) of 28% ammonia water and 32 ml (0.43 mol) of 37% formalin. The solution was heated on a water bath to 70–80°. In about 5 min a copious, slightly green precipitate began to form and the reaction mixture was heated for 2 hr. Then the mixture was left to stand at room temperature overnight and filtered. The collected precipitate was washed repeatedly with water, then with acetone, and finally with water. The wet precipitate (about 40 g) was suspended in 500 ml of water, and hydrogen sulfide gas was passed into the suspension with stirring at 40–50° for 3 hr, during which period the suspension was adjusted to pH 3–5 by the addition of concentrated hydrochloric acid. The black precipitate was filtered and washed with water. The combined orange filtrate and washings were concentrated to one-half volume and made alkaline (pH 9) with an aqueous sodium carbonate solution until an oil deposited. The oil was extracted three times with 100 ml of chloroform. After drying over anhydrous magnesium sulfate, the orange extract was concentrated using a rotary evaporator, and then the solvent was removed *in vacuo*, giving 11.5 g (70%) of the crude imidazole compound **2**. It was a very viscous, transparent, orange oil, a 75:25 mixture of the *endo*- and *exo*-imidazoles as indicated by nmr analysis: ir (neat) 3500–2200 (NH), 1580–1560 cm^{-1} (C=C and imidazole ring); nmr ($CDCl_3$) δ 12.4 (1 H, s, NH), 7.58, 7.53 (1 H, two s, N=CH—N), 6.83 (0.25 H, s, *exo*-N—CH=C), 6.63 (0.75 H, s, *endo*-NCH=C), 6.18 (1.25 H, m, C**H**=CH), 5.80 (0.75 H, dd, J = 3 and 6 Hz, CH=C**H**), 3.37 (m, H_{5x}), 3.14 (m, H_4), 2.94 (m, H_1), 2.68 (m, H_{5n}), 3.6–0.9 (7 H, m, alicyclic protons except for H_2 and H_3).

***endo*- and *exo*-5-[4(5)-Imidazolyl]bicyclo[2.2.1]hept-*exo*-2-yl Formates (3).** The crude 75:25 mixture (11.5 g; 0.072 mol) of the *endo*- and *exo*-imidazoles **2** was dissolved in 115 ml (3.1 mol) of freshly distilled 98–100% formic acid and refluxed for 50 hr. After the excess formic acid was removed using a rotary evaporator, the viscous, dark red liquid was dissolved in 100 ml of water and neutralized (pH 6) with an aqueous sodium carbonate solution. A precipitated black solid was filtered through activated carbon, and the transparent amber-colored filtrate was adjusted to pH 9. The resultant oil was extracted three times with 50 ml of chloroform, and the extract was dried over anhydrous magnesium sulfate. The solution was filtered and concentrated *in vacuo* with heating and gave 13.1 g (88%) of an orange glassy solid **3**: ir (KBr) 3500–2200 (NH), 1715 (C=O), 1570 (imidazole ring), 1170 cm^{-1} (C–O); nmr ($CDCl_3$) δ 12.40 (1 H, s, NH), 7.97 (1 H, s, CHO), 7.62 (1 H, s, N=CH—N), 6.77 (1 H, s, N—CH=C), 4.74 (1 H, m, H_{2n}), 3.12 (0.6–0.7 H, m, H_{5x}), 2.7 (m, H_{5n}), 2.45 (m, H_1 and H_4), 3.4–0.9 (9 H, m, carbocyclic ring protons except for H_{2n}); mass spectrum m/e 206 (M^+), 177 (M^+ – CHO).

Nmr analysis indicates the imidazolyl group to be 60–70% endo and 40–30% exo and the formoxy group to be 100% exo.

***endo* and *exo*-5-[4(5)-Imidazolyl]bicyclo[2.2.1]heptan-2-ones (4).** In 130 ml of reagent grade acetone 13.1 g (0.063 mol) of the crude formates **3** was dissolved together with 25 ml (H^+, 0.063 mol) of 2.5 N sulfuric acid. To this solution 33 ml of 8 N chromic acid which was prepared by the procedure of Kleinfelter and Schleyer[7] was added over 20 min with stirring at 20–25°. The reaction mixture was stirred further for 2.5 hr. On addition of 0.2 g of sodium bisulfite, no appreciable color change was observed. The mixture was diluted with 30 ml of reagent grade acetone, and the supernatant was decanted. The remaining dark solids were washed twice with acetone and the combined organic solutions were stored in a refrigerator overnight. After filtering a small amount of a yellow precipitate, the acetone solution was concentrated to about 50 ml and extracted four times with 50 ml of chloroform, and the extract was dried over anhydrous magnesium sulfate. After filtration, the solvent was removed and the residual, very viscous, and slightly orange solid was dried *in vacuo* with gentle heating, giving 8.4 g (75%) of the crude product **4**: ir (neat) 3500–2200 (NH), 1740 (C=O), 1570 cm^{-1} (imidazole ring); nmr ($CDCl_3$) δ 11.72 (1 H, broad s, NH), 7.61 (1 H, s N=CH—N), 6.85, 6.82 (1 H, two s, N—CH=C), 3.45 (0.6–0.7 H, m, H_{5x}), 3.0 (m, H_{5n}), 2.9–2.6 (m, H_1 and H_4), 3.7–1.1 (9 H, m, carbocyclic ring protons); mass spectrum m/e 176 (M^+).

Nmr analysis indicated it to be 60–70% endo and 40–30% exo for the imidazolyl group. For identification, the ketone was reacted with 2,4-dinitrophenylhydrazine in ethanol using concentrated hydrochloric acid as the catalyst. The mixture was boiled for 10 min, neutralized (pH 8), evaporated to dryness, and extracted with ethanol. After removal of the solvent, the crude crystals were recrys-

tallized from ethanol, giving yellowish-orange crystals of the 2,4-dinitrophenylhydrazone of **4**: mp 137.5–140.5°; ir (KBr) 3600–2200 (s), 1650 (w), 1620 (s), 1590 (s), 1510 (m), 1420 (m), 1335 (s), 1310 cm^{-1} (s); nmr (DMSO-d_6) δ 8.75 (1 H, dd, J = 1 and 3Hz, benzene ring proton), 8.25 (dd, J = 3 and 10 Hz, benzene ring proton), 7.75 (1 H, d, J = 10 Hz, benzene ring proton), 7.60 (1 H, s, N=CH—N), 6.86, 6.80 (1 H, two s, N—CH=C), 3.3 (0.6–0.7 H, m, H_{5x}), 8.5–5.5 (2 H, broad s, 2 NH).

Anal. Calcd. for $C_{16}H_{16}N_6O_4$: C, 53.93; H, 4.53; N, 23.58. Found: C, 53.78; H, 4.62; N, 23.61.

Nmr analysis indicated that the endo:exo ratio of the recrystallized hydrazone was almost unchanged from that of the crude ketone **4**.

***endo* and *exo*-5-[4(5)-Imidazolyl]bicyclo[2.2.1]heptan-*endo*- and *exo*-2-ols (5).** In a four-necked flask were placed 40 ml of anhydrous tetrahydrofuran and 1.1 g (29 mmol) of lithium aluminum hydride; the mixture was stirred at room temperature for 2 hr under a nitrogen atmosphere. The slurry was cooled to 0° and 3.4 g (19 mmol) of ketone **4** in 7 ml of anhydrous tetrahydrofuran was added dropwise during the course of 45 min at 2°. After stirring was continued further for 80 min at 2°, 0.6 ml of water was added to destroy the excess hydride, and then 10 ml of saturated sodium chloride solution was added. Then the mixture was adjusted to pH 9 with concentrated hydrochloric acid. The precipitated white powder was filtered and washed with tetrahydrofuran, and the combined filtrate and washings were evaporated to dryness *in vacuo* with gentle heating, giving 3.0 g (87%) of a white brittle solid of the crude alcohol **5**: ir (KBr) 3400 (OH), ~2200 (NH), 1570 cm^{-1} (imidazole ring); nmr (DMSO-d_6) δ 7.50, 7.46 (1 H, two s, N=CH—N), 6.78, 6.68 (1 H, two s, N—CH=C), 6.4 (4 H, broad s, NH, OH, and moisture), 4.02 (*ca.* 0.9 H, m, H_{2x}), 3.6 (m, H_{2n}), 3.2–2.7 (m, H_{5x} and H_{5n}).

The endo:exo ratios of the hydroxyl and imidazolyl groups were determined from the nmr spectrum of the *O*-acetoxy derivative, because it was difficult to analyze the nmr spectrum of the crude alcohol **5** quantitatively. The *O*-acetoxy derivative was prepared using acetic anhydride according to the method of Bruice and Sturtevant:[12] ir (neat) 3400–2200 (NH), 1730 (C=O), 1570 cm^{-1} (imidazole ring), 1250 cm^{-1} (C–O); nmr ($CDCl_3$) δ 12.70 (1.5 H, broad s, NH and moisture), 7.63, 7.62 (1 H, two s, N=CH—N), 6.90, 6.76 (1 H, two s, N—CH=C), 4.96 (0.9 H, m, H_{2x}) 4.60 (0.1 H, m, H_{2n}), 3.5–2.7 (*ca.* 1 H, m, H_{5x} and H_{5n}), 2.03 (3 H, s, CH_3CO).

***endo*-5-[4(5)-Imidazolyl]bicyclo[2.2.1]heptan-*endo*-2-ol (6).** The isolation of **6** from **5** was achieved by preparative tlc. About 240 g of basic alumina from Merck (HF_{254} type E) was coated on ten glass plates (20 × 20 cm) and activated as indicated by Merck. To these plates 1003 mg of the reduction product **5** dissolved in a small amount of anhydrous methanol was applied and developed three times using a 20:1 mixture of dichloromethane and methanol (by volume) as eluent. Four bands were observed and their R_f values and band widths were as follows: 0.09 (2.5 cm), 0.24 (1.5 cm), 0.46 (1.8 cm), and 0.55 (0.3 cm). They were extracted three times with anhydrous methanol, and the components obtained after drying *in vacuo* weighed 30, 449, 276, and 30 mg, respectively. The third component (276 mg, R_f 0.46) was identified as **6**: ir (neat) 3500–3000 (OH), ~2200 (NH), 1570 cm^{-1} (imidazole ring); nmr (DMSO-d_6) δ 7.52 (1 H, s, N=CH—N), 6.78 (1 H, s, N—CH=C), 6.5 (broad s, NH, OH, and moisture), 4.05 (1 H, m, H_{2x}), 3.10 (1 H, m, H_{5x}), 2.25 (2 H, m, H_1 and H_4), 2.4–0.8 (8 H, m, alicyclic protons except for H_{2x} and H_{5x}). The first and fourth components were mixtures of the imidazole compounds and impurities. The second (449 mg, R_f 0.24) was identified as **7**: ir (neat) 3500–3000 (OH), ~2200 (NH), 1570 cm^{-1} (imidazole ring); nmr (DMSO-d_6) δ 7.52 (1 H, s, N=CH—N), 6.82 (trace, s, *endo*-NCH=C), 6.72 (1 H, s, *exo*-N—CH=C), 6.6 (broad s, NH, OH, and moisture), 4.07 (*ca.* 0.8 H, m, H_{2x}). 3.60 (*ca.* 0.2 H, m, H_{5x}), 3.10 (trace, m, H_{5x}), 2.70 (1, H, m, H_{5n}), 3.0–0.8 (9 H, m, carbocyclic protons except for H_2).

***endo*-5-[4(5)-Imidazolyl]bicyclo[2.2.1]hept-*endo*-2-yl *trans*-Cinnamate (8).** In 4 ml of chloroform, which was washed with water and distilled to remove ethanol as stabilizer, 204 mg (1.12 mmol) of **6** was dissolved. To this solution 450 mg (2.7 mmol) of *trans*-cinnamoyl chloride was added, and the solution was refluxed for 90 min at 80–90°. The homogeneous solution was diluted with chloroform, washed with aqueous potassium hydrogen carbonate solution, and evaporated *in vacuo*. An attempt was made to dissolve the residual solid in dilute hydrochloric acid with gentle warming, but only a small amount of the solid dissolved. This dissolved solid was recovered after neutralization (52 mg) and found to contain traces of *exo*-imidazolyl and *exo*-acyloxy groups. The insoluble crystalline solid was recrystallized from chloroform–ether, giving 330 mg of white crystalline material, mp 274–275.5°. Nmr and ir spectra indicated it to be the *O*- and *N*-diacylated compound (both 100% endo). It was dissolved in a mixture of 15 ml of chloroform and 55 ml of methanol. After addition of 20 ml of water, the solution was acidified (pH 3) with hydrochloric acid and allowed to stand at 0° overnight. The hydrolyzed solution was evaporated to about 20 ml and the residual milky mixture was washed twice with ether. The clear solution was adjusted to pH 9 with an aqueous sodium carbonate solution and extracted twice with chloroform. After drying over anhydrous magnesium sulfate, the solvent was removed *in vacuo*, giving 211 mg of a colorless brittle solid. It was crystallized from a minimum volume of chloroform by addition of ether and scratching, giving 186 mg of white crystalline material (dried *in vacuo* at 80° for 2 hr), mp 130–132°; ir (KBr) 3400–2200 (NH), 1703 (C=O), 1635 (C=C), 1575 (imidazole ring), 1185 cm^{-1} (C–O); nmr ($CDCl_3$) δ 9.7 (1 H, s, NH) 7.67 (1 H, d, J = 16 Hz, C**H**=CH), 7.54 (1 H, s, N=CH—N), 7.7–7.2 (5 H, m, phenyl ring protons), 6.92 (1 H, s, N—CH=C), 6.38 (1 H, d, J = 16 Hz, CH=C**H**), 5.09 (1 H, m, H_{2x}), 3.28 (1 H, m, H_{5x}), 2.53 (2 H, m, H_1 and H_4), 2.2–0.9 (6 H, m, H_{3x}, H_{3n}, H_{6x}, H_{6n}, $H_{syn\text{-}7}$, and $H_{anti\text{-}7}$).

Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 73.92; H, 6.45; N, 9.14.

***exo*-5-[4(5)-Imidazolyl]bicyclo[2.2.1]hept-*endo*-2-yl *trans*-Cinnamate (10).** In 8 ml of the purified chloroform, 382 mg (2.15 mmol) of **7** was dissolved. To this solution 860 mg (5.1 mmol) of *trans*-cinnamoyl chloride was added, and the solution was refluxed for 60 min at 75–80°. The homogeneous solution was evaporated, and the residual solid was dissolved in 5 ml of water with gentle warming. A remaining oil was extracted with chloroform and the aqueous solution was adjusted to pH 9 with potassium hydrogen carbonate. The deposited material was extracted with chloroform, giving a slightly yellow solution. After drying over anhydrous magnesium sulfate, the solvent was removed to give 755 mg (theory, 660 mg) of residual material. It was dissolved again in dilute hydrochloric acid, and the insoluble material was filtered through activated carbon. The slightly yellow clear filtrate was treated as before, giving 541 mg of a colorless brittle solid. Nmr analysis indicated it to be the *O*-acylated derivative of **7**. Onto a column containing 125 g of basic alumina (Merck, activity I) (2.4-cm diameter, 30-cm height), 412 mg of the above ester was poured and eluted with a 3:10 mixture of methanol and dichloromethane. The first 70 ml of the eluent contained nothing. The second 32-ml portion of the eluent contained 40 mg, the third 12-ml portion 16 mg, the fourth 16-ml portion 50 mg, the fifth 20-ml portion 53 mg, the sixth 80-ml portion 81 mg, and the seventh 112-ml portion 63 mg of the solute. Further, 16 mg of a solid was recovered from 185 ml of a 1:1 mixture of the two solvents. Nmr analysis indicated that the first and last components were (unidentified) impurities. The third component was discarded because it had a higher percentage of the *endo*-imidazolyl and *exo*-acyloxy groups than the others. Therefore, the fourth, fifth, and sixth portions were combined (197 mg). Almost the same combined material (59 mg) was obtained from 129 mg of the ester using a column of 1.3-cm diameter and 18.5-cm height containing 25 g of alumina. Both the components were combined and crystallized as in the case of **8**, giving 198 mg of white crystalline material. Recrystallization was repeated twice, and finally, 127 mg of white crystals was obtained from chloroform–carbon tetrachloride (dried *in vacuo* at 80° for 4.5 hr):[13] mp 174–176° dec; ir (KBr) 3400–2200 (NH), 1718 (C=O), 1640 (C=C), 1578 (imidazole ring), 1185 cm^{-1} (C–O); nmr ($CDCl_3$) δ 8.75 (1 H, s, NH), 7.68 (1 H, d, J = 16 Hz, C**H**=CH), 7.57 (1 H, s, N=CH—N), 7.7–7.2 (5 H, m, phenyl ring protons), 6.77 (1 H, s, N—CH=C), 6.42 (1 H, d, J = 16 Hz, CH=C**H**), 5.12 (1 H, m, H_{2x}), 2.93 (1 H, m, H_{5n}), 3.1–1.0 (9 H, m, carbocyclic protons except for H_{2x}).

Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08 (same as **8**). Found: C, 73.98; H, 6.55; N, 9.32.

Registry No.—*endo*-**1**, 52747-94-1; *exo*-**1**, 52747-95-2; *endo*-**2**, 52747-96-3; *exo*-**2**, 52747-97-4; *endo*-**3**, 52747-98-5; *exo*-**3**, 52759-86-1; *endo*-**4**, 52747-99-6; *endo*-**4** 2,4-DNP, 52748-00-2; *exo*-**4**, 52748-01-3; *exo*-**4** 2,4-DNP, 52748-02-4; **6**, 52748-03-5; **6** *O*-acetoxy derivative, 52748-04-6; *ezo*-**7**, 52748-05-7; *exo*-**7** *O*-acetoxy derivative, 52748-06-8; *endo*-**7**, 52759-87-2; *endo*-**7** *O*-acetoxy derivative, 52759-88-3; **8**, 52748-07-9; **10**, 52759-89-4; formic acid, 64-18-6; *trans*-cennamoyl chloride, 17082-09-6.

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(13) It was imperative to use ethanol-free chloroform for recrystallization.

Notes

Selective Chemical Ionization Mass Spectrometry as an Aid in the Study of Thermally Labile Three-Membered Ring Sulfones

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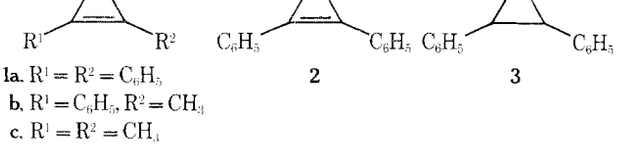
Recently a theoretically interesting group of compounds has been synthesized in which a sulfur has been incorporated in a three-membered ring.[1] The structures of these unusual compounds have been established by a combination of spectroscopic and chemical data. However, verification of the molecular weight of the sulfones **1a–1c** by mass spectrometry, employing the conventional electron impact (EI) ionization method, has been unsuccessful because of the absence or insignificant intensity of molecular ion peaks in their mass spectra. The base peak in the electron impact mass spectra of **1a–1c**, as well as the related compounds **2** and **3**, corresponds to the formation of the disubstituted acetylene ion $[(R^1\text{–}C{\equiv}C\text{–}R^2)\cdot^+]$.



1a. $R^1 = R^2 = C_6H_5$
b, $R^1 = C_6H_5$, $R^2 = CH_3$
c, $R^1 = R^2 = CH_3$

2 **3**

No molecular ion peaks could be detected in the EI mass spectra of **1a** or **1b**, although very weak ones were observed in the mass spectra of the other compounds (see Table I).

Decomposition of the molecular ions in the EI spectra of **1–3** is particularly favorable because of the facile expulsion of the neutral species SO_2, SO, and CO, respectively. Indeed, in the sulfone case, considerable thermal decomposition may precede ionization as suggested by the fact that only the most volatile of the sulfones examined (**1c**) gave any evidence for a molecular ion. These sulfones generally undergo thermal fragmentation at approximately 100–125° at atmospheric pressure, and consequently we decided to investigate the mass spectrometry of these compounds under carefully controlled experimental conditions.

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Table I
Relative Abundance of Molecular Ionic Species in the EI and CI Spectra of 1–3.

Compd	EI	CI CH_4	CI isobutane	CI NH_3	CI $NHMe_2$
1a				0.2,[b] 2.9[c]	23[d]
1b				2,[b] 21[c]	42[d]
1c	0.12[a]	16[b]	42[b]	0.5,[b] 86[c]	70[d]
2	0.25[a]	26[b]	49[b]	24,[b] 3[c]	69[d]
3	0.10[a]	15[b]	81[b]	45,[b] 9[c]	75[d]

[a] Refers to %Σ of $M\cdot^+$. [b] Refers to %Σ of $(M + H)^+$ ion. [c] Refers to %Σ of $(M + NH_4)^-$ ion. [d] Refers to %Σ of $(M + NH_2Me_2)^+$ ion.

Results and Discussion

Lowering of the ionizing energy to ~10 eV in combination with lower ion source and inlet probe temperatures (<100°) failed to enhance significantly the relative abundance of the molecular ion in the EI spectra of **1–3**, and thus it became apparent that alternative ionization methods had to be considered. In view of the relatively lower energy processes involved in chemical ionization (CI) mass spectrometry,[2,3] we have explored the application of this technique as a means of determining the molecular weights of such unstable compounds. Chemical ionization spectra of **1–3** were obtained with various reagent gases and they are partially summarized in Table I. As a representative example, the complete EI and CI mass spectra of **1a** are compared in Figure 1. In all cases, the ion source temperature was kept at the lowest possible level required for sample vaporization to minimize possible thermal decomposition effects. The heat transmitted from the ion source of the CEC 21-110B mass spectrometer was sufficient for vaporization of the samples, and consequently no further heating of the solid inlet probe was necessary.

The methane CI spectra of **1a–1c** and **2** are dominated by the $(R^1C{\equiv}CR^2 + H)^+$ ion which carries approximately 55, 57, 60, and 26% of the total ion current in the case of **1a**, **1b**, **1c**, and **2**, respectively. As was the case with electron impact ionization, no molecular ion species were detected in the methane CI spectra of **1a** and **1b** at *m/e* values corresponding to $(M + H)^+$. The presence of the SO_2 function in the sulfones **1a–1c** is evident, however, from the intense *m/e* 65 peak corresponding to $(SO_2 + H)^+$, and which carries 22, 23, and 9% of the total ion current in **1a**, **1b**, and