

I. CRYSTAL STRUCTURE OF A NORDITERPENE DILACTONE;

II. CMR SPECTRA OF ANALGESICS

by

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APPROVAL BY THESIS DIRECTOR

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Date

To Wen-Chin and My Parents

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## ABSTRACT

I. The crystal structure of sellowin B bromohydrin acetate has been determined by X-ray diffraction. The space group is  $P2_1$  with cell dimensions  $a = 10.060(5)$ ,  $b = 6.127(4)$ ,  $c = 16.037(6)\text{\AA}$ ,  $\beta = 96.02(2)^\circ$ , and  $Z = 2$ . The torsion angles reveal that rings A, B and C have chair 1,2-diplanar (sofa) and 1,3-diplanar conformations, respectively. The structure was solved by an acentric direct method program, MULTAN, and was refined by the full matrix least squares method to a final  $R$  value of 0.053. The structure indicates sellowin B and related compounds to be 2,3- $\beta$ - rather than 1,2- $\alpha$ - epoxides. Earlier chemical results are interpreted in light of the new structure.

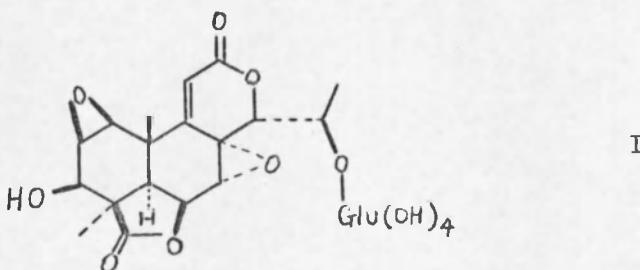
II. Carbon-13 chemical shifts were measured for 26 synthetic analgesics related to morphine. The signal due to each carbon was assigned. The  $^{13}\text{C}$  assignments of the protonated carbons were greatly aided by single frequency off-resonance decoupling experiments.

## PART I

### CRYSTAL STRUCTURE OF A NORDITERPENE DILACTONE

#### Introduction

Podocarpus species are known to produce nor- and bisnorditerpene dilactones,<sup>1</sup> some of which are potent inhibitors of expansion and mitosis of plant cells. An example is inumakilactone A 15- $\beta$ -D-GLucoside(I) from the stem of Podocarpus macrophyllus D. Don.<sup>2</sup>

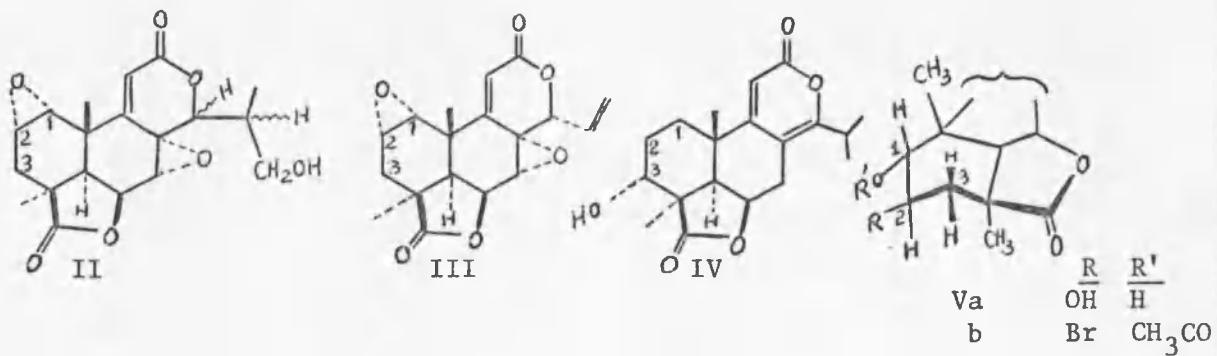


The chemical reactions of those polyfunctional substances give many unexpected results, making structures deduced by chemical methods open to question. Starting material is frequently recovered, even under vigorous reaction conditions.\* The lactone and epoxide groups show<sup>3</sup> unusual stability to many acids and bases. Hydroxyls are often sterically protected from attack by normal reagents, and even a vinyl group resists well-known double bond attacking reagents such as diborane and mercuric acetate.<sup>4</sup> The insolubility of many of the compounds in any solvent other than pyridine, dimethylsulfoxide, or acetone has undoubtedly also contributed to the paucity of chemical transformations reported.

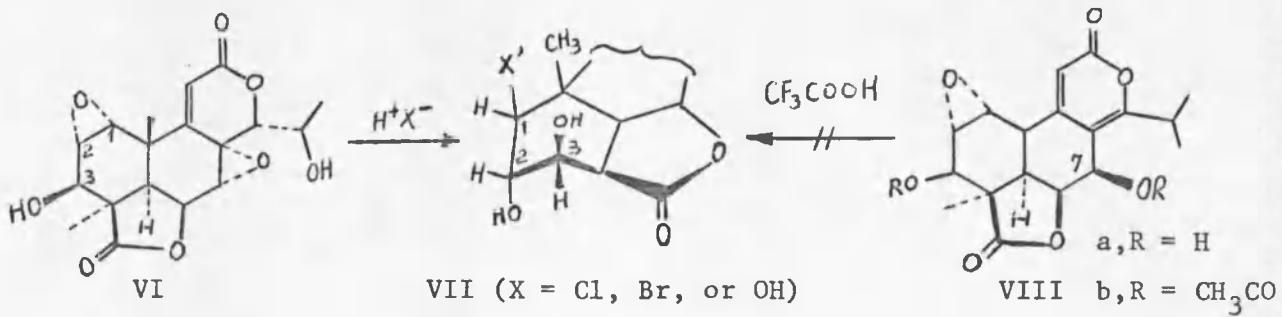
\*The failure of standard reactions on 16-sulfoxides (podolactone C and D) has been reported<sup>3</sup>.

In the course of several years' work on compounds termed sellowins A, B, and C isolated from the Brazilian Podocarpus Sellowii Klotzsch, Dr. Keith Brown and coworkers observed reactions which together with spectral measurements and analogy with structures deduced for other *Podocarpus* dilactones led them to propose structures II-IV, respectively, for these compounds.<sup>5</sup> Some of these reactions merit discussion here, as they led to what later proved to be incorrect structures.

Certain acid conditions gave selective attack on the epoxy group in ring A of sellowins A(II) and B(III) without affecting the other epoxide in the molecule. For example, solation of Sellowin B(III) in trifluoroacetic acid gave slow modification of the portion of the NMR spectrum corresponding to the ring A protons, with formation of an easily hydrolyzed diol monotrifluoroacetate ( $M^+ 444 = C_{20}H_{19}O_8F_3$ ). The corresponding diol showed coupling of the  $2\alpha$ -proton ( $\delta 4.36$  in pyridine-d<sub>5</sub>) to the  $1\beta$ -proton ( $\delta 3.84$ ) with  $J=11$  Hz, and to the  $3\beta$  and  $3\alpha$  proton with  $J=12.5$  and 5 Hz, respectively, showing that the first three of these protons possess approximately trans antiparallel relative dispositions. This requires a twist-boat conformation for ring A (Va). Indeed, a Dreiding model of V with ring A in the chair conformation either opens or flips to a twist-boar with great ease, independent of substitution at C-2.

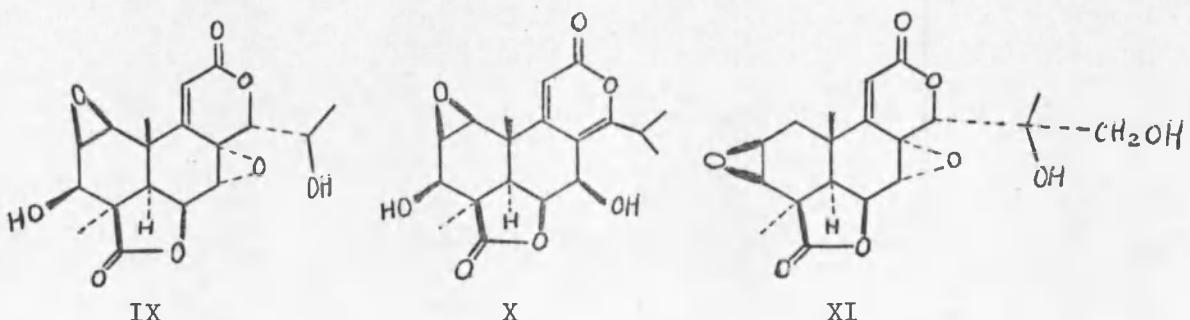


Attempted bromohydrin formation by electrophilic attack on the vinyl group of sellowin B(III) with N-bromoacetamide in 90% aqueous acetone gave very slow reaction, producing a substance which still possessed the vinyl group (by NMR) but was nevertheless a bromohydrin (IR). The more tractable derived acetate showed coupling patterns for the  $1\beta$  ( $\delta$  5.66 in pyridine-d5),  $2\alpha$  ( $\delta$  4.74), and  $3\beta$  and  $3\alpha$  protons identical to those observed in diol Va, indicating structure Vb. In both cases, attack of the nucleophile at the exposed  $\alpha$ -position of the protonated epoxide apparently occurred (the bromohydrin was apparently formed by slow release of HBr from the N-bromoacetamide reagent, to whose attack the vinyl group was resistant). This contrasted with the results published<sup>6</sup> for acid opening of the ring A epoxide in inumakilactone A (believed at that time to be VI) and related compounds, which apparently gave VII by selective attack at the 1 - position. In this case, the different regiospecific control of the reaction was believed to be provided by interaction of the nucleophile with the 3 -hydroxyl group in VI. Interestingly, attempted opening of the analogous epoxide in nagilactone C (postulated to be VIIIa) with trifluoroacetic acid (as used for sellowin B-III) led quantitatively to the 7-O-monotrifluoracetate, leaving the epoxide intact.



However, two recent X-ray analyses have indicated that the majority of the published structures<sup>7</sup> in the group require revision. Thus, inumakilactone A, long supposed to possess structure VI with a 1,2- $\alpha$ -epoxide in ring A<sup>8</sup>, was shown by X-ray analysis to be in fact a 1,2- $\beta$ -epoxide IX<sup>9</sup>. This structural modification affected, by extension, the accepted structures of at least ten other compounds isolated from eight Podocarpus species in three continents and New Zealand, including the most widely distributed member of the group, nagilactone C (formerly VIIIa, but now presumably X<sup>7,9,10</sup>). By X-ray analysis of its p-bromobenzoate, podolactone A was shown to be a 2,3- $\beta$ -epoxide XI<sup>11</sup> rather than the 1,2- $\alpha$ -epoxide widely accepted<sup>7,12</sup>. By extension, at least five additional lactones from three podocarpus species, including sellowins A-C (proposed to be II-IV), might require similar modification.

The present study, consisting of an X-ray study of a crystalline derivative of sellowin B (III) was undertaken to establish the structure of this substance and, by analogy, the other sellowins (II and IV).



Reaction of sellowin B (III)<sup>4,5,7</sup> with N-bromacetamide under forcing conditions, in an attempt to functionalize the double bond and thereby give entry to a three-carbon side chain, gave exclusively a

hygroscopic ring A bromohydrin, m.p. 204-208°, which was directly acetylated to a beautifully crystalline bromohydrin acetate. This compound was selected for X-ray analysis over the less satisfactorily crystalline tribromide (olefin dibromide + epoxide bromohydrin) produced by direct bromination of sellowin B (III).

### Experimental

#### Preliminary Investigation

Crystals of sellowin B bromohydrin acetate obtained from Dr. Brown were recrystallized from acetone and a single crystal of dimensions  $0.2 \times 0.2 \times 0.4$  mm was mounted about the needle axis (b). An oscillation photograph showed bilateral symmetry, but there was no symmetry in the corresponding Weissenberg photograph. This indicated that the crystal belonged to the monoclinic system. The number of molecules in the unit cell calculated from the cell volume and the experimental density was 2. The zero level, 1st level and 2nd level Weissenberg photographs showed that there were no systematic absences in  $h k \ell$ ,  $k 0 \ell$ ,  $0 k \ell$ ,  $h k 0$ ,  $h 0 0$ , and  $0 0 \ell$ . This indicates the space group is either Pm, P2, or  $P2_1$ . After mounting another crystal along the a axis and taking a zero level Weissenberg photograph it was observed that only  $0 k 0$  reflections with  $k = 2n$  were present, so it concluded that the space group was  $P2_1$  (no. 4 in International Tables for Crystallography Vol. I).

This space group has a twofold screw axis and the equivalent positions  $x, y, z$  and  $\bar{x}, 1/2 + y, \bar{z}$ .

### Data Collection

Intensity data were collected on a Picker FACS-I four-circle computer-controlled diffractometer. The term "four-circle" arises from its possession of four arcs which may be used to adjust the orientation of the crystal so as to bring any desired plane into reflection position. The crystal orienter contains the  $\phi$  and  $\chi$  circles, and the base contains the  $\omega$  and  $2\theta$  circles, as shown in Figure 1.

An incident beam monochromator equipped with a graphite crystal was used to obtain Cu K<sub>α</sub> radiation,  $\lambda = 1.54178\text{\AA}$ . A scintillation counter with pulse-height analyzer was used to record intensities of diffracted beams. Background counts of ten seconds were taken at both ends of the scan ( $\theta - 2\theta$ ) after scanning the reflection at a rate of  $2^\circ/\text{min}$ . When the counting rate exceeded 10,000 cps, metal foil attenuators were automatically inserted. A dispersion factor allowing for  $\alpha_1 - \alpha_2$  splitting at large  $2\theta$  values was used. Of 1620 independent reflections measured,  $1591 > 3\sigma (I)$  were considered observed. Throughout the data collection, reflections 4 0 7, 0 -4 0, and 0 0 10 were monitored as standards.

Lorentz and polarization corrections were applied, but no correction was made for absorption.

The most accurate unit cell parameters were determined by least-squares refinement of the settings for four angles of ten reflections that had been accurately centered, and were found to  $a = 10.060(5)$ ,  $b = 6.127(4)$ ,  $c = 16.037(6)\text{\AA}$ ,  $\beta = 96.02(2)^\circ$ ,  $P_c = 1.53 \text{ g/ml}$ .

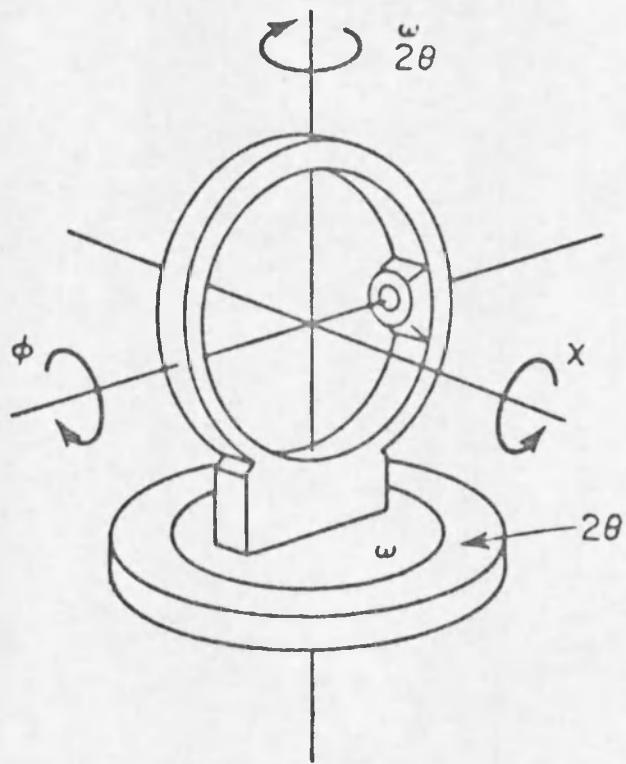


Figure 1. Circle designations on a four-circle diffractometer.

## Structure Solution and Refinement

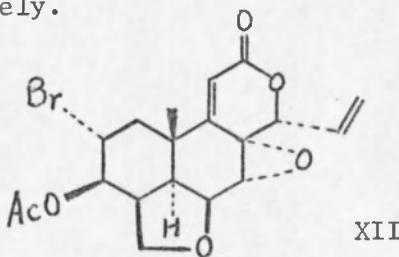
Phases for reflections with normalized structure factor  $E > 1.4$  were used to solve the structure using the program MULTAN<sup>13</sup>.

The first E map revealed Br and a seven carbon atom fragment. The R factor at this stage was 0.360. The rest of the nonhydrogen atmosphere located using difference Fourier synthesis. After four cycles of full matrix least-squares refinement of nonhydrogen atoms using isotropic thermal parameters, the R value was 0.160. Four more cycles of full-matrix least-squares refinement with anisotropic temperature factors reduced R to 0.071. At this point all twenty hydrogen atoms were located on a difference map. Two more cycles of least-squares refinement using anisotropic temperature factors for nonhydrogen atoms reduced R to the final value of 0.053. The refinement was terminated at this stage since the ratios of shifts in parameters to estimated standard deviations were all less than 0.3. The refinement was based on  $F_o$ , the quantity minimized being  $\Sigma w (F_o - F_c)^2$ . The weighting scheme used was based on counter statistics Corfield, Doedens and Ibers<sup>14</sup>; the value of P was 0.04. The scattering factors used were those of H. P. Hanson, F. Herman, J. D. Lea, and S. Skillman.<sup>15</sup>

## Results and Discussion

This X-ray analysis of the bromohydrin acetate revealed it to possess structure XII. The final atomic positional parameters are given in Table A-1, and final thermal parameters of the atoms with estimated standard deviations are listed in Table A-2. The numbering system for atoms is shown along with bond length and angles for nonhydrogen atoms.

in Figure 2. The carbons are numbered 1-21 (exclusive C<sub>13</sub>), hydrogens have the same numbering as the carbon to which they are attached, and oxygens are numbered 13-19. The C - H distances are in Table A-3 and bond distances involving hydrogens are in Table A-4. The average standard deviations in Br-C, C-C, and C-O bond lengths are 0.007, 0.008, and 0.009 $\text{\AA}$ , respectively. The corresponding estimated standard deviations in Br - C - C, C - C - C, and C - C - O bond angles are 0.4, 0.5, and 0.5°, respectively.



The conformation of the molecule is depicted in Figure 3. The torsion angles in the rings are given in Table A-5, and show that rings A, B, and C have chair, 1,2 - diplanar, and 1,3 - diplanar conformations, respectively.<sup>16</sup> Five-membered ring D has an envelope (Cs) conformation. The torsion angles involving the acetate group are C<sub>2</sub> - C<sub>13</sub> - O<sub>17</sub> - C<sub>17</sub> (124.7°), C<sub>4</sub> - C<sub>3</sub> - O<sub>17</sub> - C<sub>17</sub> (-108.4°), C<sub>3</sub> - O<sub>17</sub> - C<sub>17</sub> - C<sub>21</sub> (-174.8°), and C<sub>3</sub> - O<sub>17</sub> - C<sub>17</sub> - O<sub>18</sub> (4.0°). The shortest intermolecular distance between two nonhydrogen atoms (O<sub>16</sub> - C<sub>19</sub>) is 1.203 $\text{\AA}$ . The shortest intermolecular distance between a hydrogen and nonhydrogen atom (H<sub>1</sub> - C<sub>18</sub>) is 0.73 $\text{\AA}$ .

Observed and calculated structure factors are listed in Table A-6.

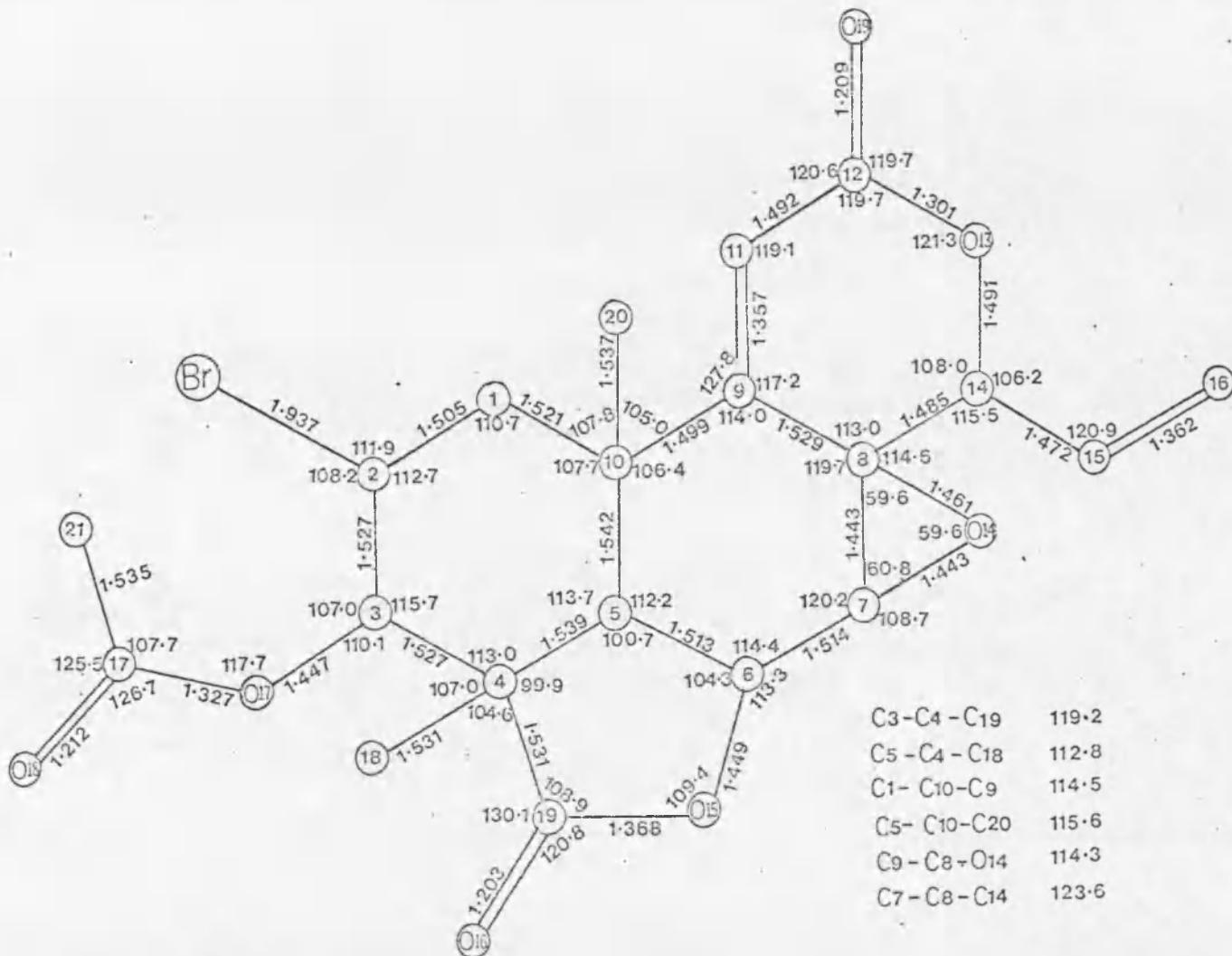


Figure 2. Bond lengths (Å) and bond angles (°) in the molecule, with standard deviations in Br-C, C-C, and C-O lengths of 0.007, 0.008, and 0.009 Å, respectively, and in Br-C-C, C-C-C, and C-C-O angles of 0.4, 0.5, and 0.5°, respectively.



Figure 3. Stereoscopic view of the molecule.

Hydrogen atoms are depicted as spheres, and other atoms as 50% probability ellipsoids.

The structure XII revealed by the X-ray study for the bromohydrin acetate leaves no doubt that the correct structure for sellowin B is XIII, identical to the published structure in all details except for the position and configuration of the ring A epoxide. This corresponds to the modification required in podolactone A(XI).<sup>11</sup> (This can be extended to podolactone C XIV because of the extremely close similarity of chemical shifts and coupling constants for the ring A protons in the NMR spectra of the two compounds<sup>3</sup>, and because the two lactones coexist in P. neriifolius.)

By arguments similar to the above, the revised ring A structure can be extended from sellowin B (XIV) and also hallactone B(XVb)<sup>17</sup>, which is obtained by oxidation of podolactone C (XVa)<sup>3</sup>. The NMR spectra of the latter compound in DMSO and pyridine, however, are more suggestive of the presence of at least one  $\beta$ -proton on the epoxide.<sup>7</sup> This may be simply another case of the unusual spectral characteristics of these compounds, which seem to obey few of the rules derived from observation on less polar natural products with more scattered functional groups.

The direction of opening of the epoxide ring in sellowin B (XIII) to give after acetylation bromoacetate XII violates the axial attack rule, and is probably the result of unfavorable steric interactions ( $C_{18}$  methyl group with bromine,  $C_{20}$  methyl group with the developing hydroxyl group) in the transition state leading to the unobserved bromohydrin. The observed produce results from ring opening to a twist-boat conformation (XVI,  $X=Br$   $Y=H$ ), which quickly equilibrates to a chair conformatin similar to that depicted in Figure 3. Figure 4 gives packing in the unit cell.

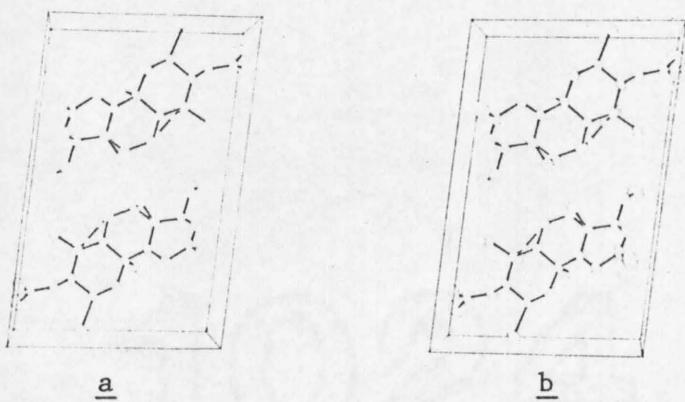
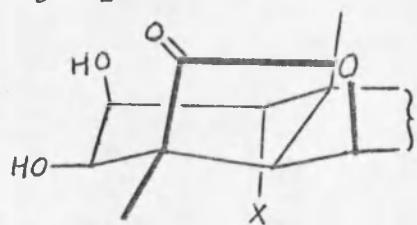
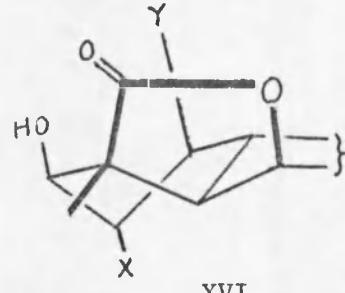
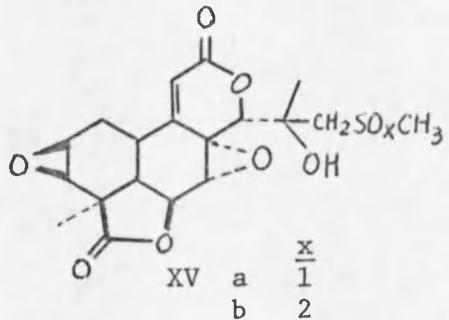
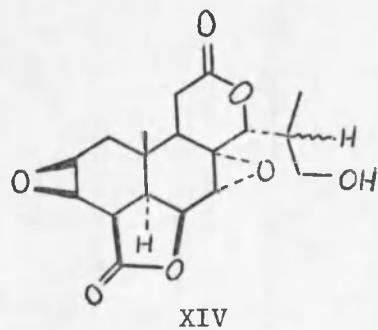
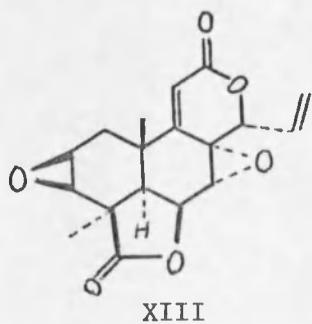
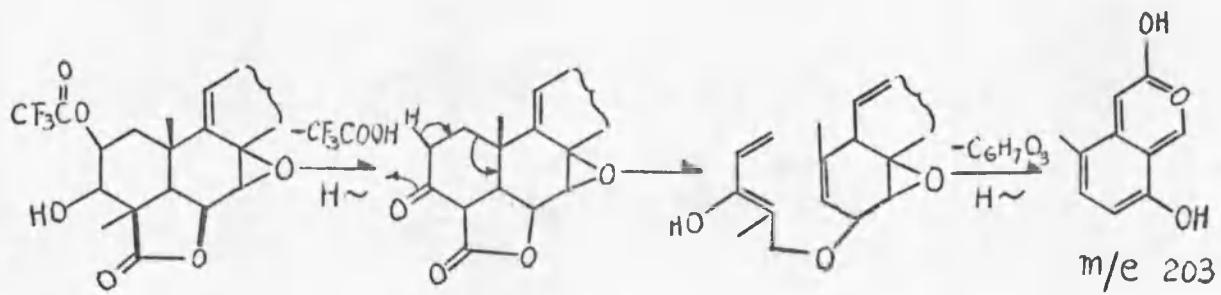


Figure 4. Stereoscopic view of a unit cell, b axis projection, a axis horizontal.



XVII

SCHEME 1

Sellowin B + trifluoracetic acid

The correction in the stereochemistry of inumakilactone A(IX)<sup>10</sup> also requires modification of the stereochemistry of its 1,2-epoxide ring opening products, which from the reported pmr coupling constants<sup>6</sup> must be represented by either XVI or XVII (X=Br, Cl, or OH; Y=OH). XVII, the product of axial attack, fits the observed pmr constants, but so does XVI (Y=OH) provided that it remains predominantly in the twist-boat conformation.

The published mass spectral fragmentation schemes for sellowin B (XIII) and derivatives<sup>4</sup> are not substantially changed by the modification in its structure; even the retro-Diels-Alder cleavage of ring A can proceed in identical fashion through an enol, or in slightly modified form through a ketone, as in Scheme 1.

## PART II

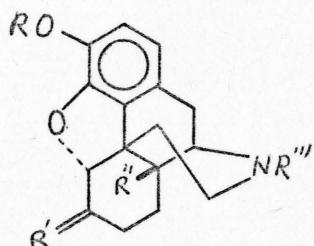
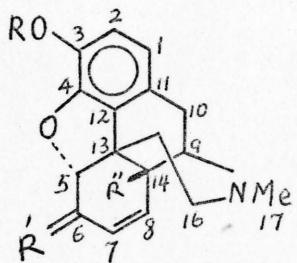
### CMR SPECTRA OF ANALGESICS

#### Introduction

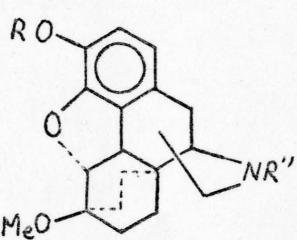
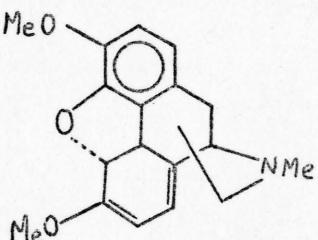
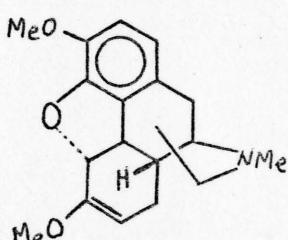
Recently, Terui and coworkers reported CMR spectral shifts on morphine (1a) derivatives 1b, 1f, 1i, 2a, 2c, 2d, 3, 4, 7, 8, and 9a-g as summarized in Table B-1<sup>18</sup>. Carroll and coworkers have measured the CMR shifts for morphine derivatives 1a-d, 2b-d, and 4 (Table B-2)<sup>19</sup>, 14-hydroxymorphines 1e-h and 2e-i (Table B-3), 6,14-endo-ethanotetrahydrothebaines (5a-d), and 6,14-endo-ethenotetrahydrothebaines (6a-d) in Table B-4.

We wish to report a related study in which we have assigned CMR shifts to 26 synthetic analgesics related to morphine (1a). The previous studies were performed on the free bases in organic solvents whereas ours were done on the ammonium salts in D<sub>2</sub>O. In only two cases (2f with 2l, 2g with 2m) does our study overlap with the earlier work. Our samples, obtained from Dr. Robert Katz (Mid-Atlantic Research Institute) were EN 1620A-HCl(2j), EN 2234A-HCl(2k), Naloxon-HCl(2l), Naltrexone-HCl(2m), EN 1655A-HCl(2n), EFH-I-27-2HCl(2o), Oxilorphan Tartrate(9h), Butorphanol Tartrate(9i), Levallorphan Tartrate(9j), R-04-0287-HCl(9k), Mr 1256-Ms Methanesulfonate(10a), Mr 1405-C1-HCl(10b), Mr 1268-Ms Methanesulfonate(10c), Mr 1029-Ms Methanesulfonate(10d), Cyclazocine-HCl (10e), Pentazocine(+)-HCl(10f), Pentazocine Norbase-HCl(10g), Ab-2P-173 Methanesulfonate(10h), B01-N-196 Methanesulfonate(10i), GPA 1467(+)-HCl

(10j), GPA 1866(10k), PD1 Monosuccinate(11a), PD2 Monosuccinate(11b), PD3-HCl(11c), PD6-HCl(11d), and Norketobemidone(12).



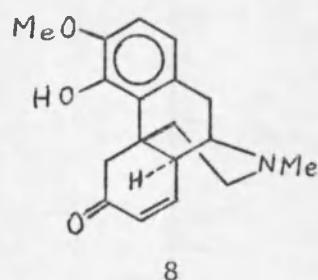
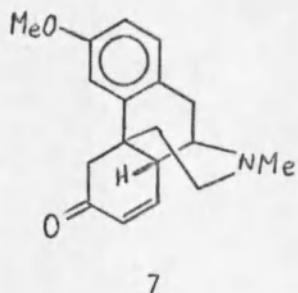
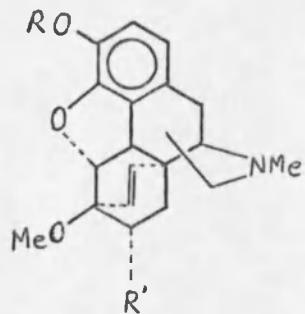
	<u>R</u>	<u>R'</u>	<u>R'''</u>		<u>R</u>	<u>R'</u>	<u>R'''</u>	<u>R''''</u>
1a	H	--OH	H (Morphine)		2a	Me	H <sub>2</sub>	Me
b	Me	--OH	H (Codeine)		b	H	--OH	Me
c	Ac	--OAc	H		c	Me	--OH	Me
d	H	--OAc	H		d	Me	=O	Me
e	H	=O	OH		e	Me	=O	H
f	Me	=O	OH		f	H	=O	OH
g	Ac	=O	OAc		g	H	=O	Cyclopropylcarbinyl
h	Me	=O	OAc		h	H	--OH	Cyclopropylcarbinyl
i	Me	=O	H		i	H	-OH	Cyclopropylcarbinyl
					j	H	=O	$\gamma,\gamma$ -Dimethylallyl,H <sup>+</sup>
					k	H	-OH	Cyclobutylcarbinyl,H <sup>+</sup>
					l	H	=O	Allyl,H <sup>+</sup>
					m	H	=O	Cyclopropylcarbinyl,H <sup>+</sup>
					n	H	=O	Cyclobutylcarbinyl,H <sup>+</sup>
					o	H	=CH <sub>2</sub>	Allyl,H <sup>+</sup>



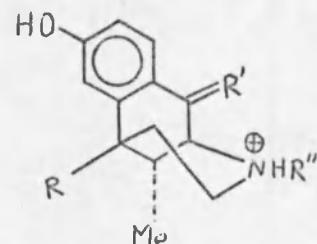
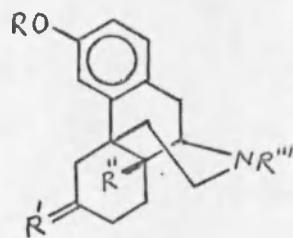
3

4

	<u>R</u>	<u>R'</u>	<u>R'''</u>
5a	Me	Ac	Me
b	H	CMe <sub>2</sub> OH	Cyclopropylcarbinyl
c	Me	CMe <sub>2</sub> OH	Me
d	Me	CMe <sub>2</sub> OH	CN



	<u>R</u>	<u>R'</u>
6a	Me	Ac
b	H	CMePrOH
c	Me	CMe <sub>2</sub> OH
d	Me	CMePrOH

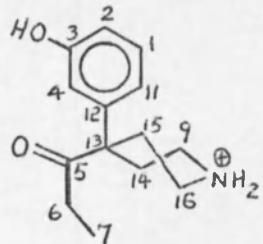
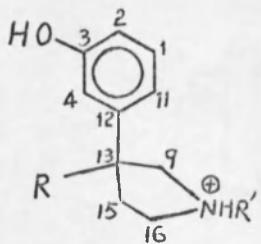


	<u>R</u>	<u>R'</u>	<u>R''</u>	<u>R'''</u>
9a	Me	H <sub>2</sub>	H	H
b	Me	H <sub>2</sub>	H	Me
c	Me	--OH	H	Me
d	Me	-OH	H	Me
e	Me	=O	H	H
f	Me	=O	H	Me
g	Me	=O	OH	Me
h	H	H <sub>2</sub>	OH	Cyclopropylcarbonyl, H <sup>+</sup>
i	H	H <sub>2</sub>	OH	Cyclobutylcarbonyl, H <sup>+</sup>
j	H	H <sub>2</sub>	H	Allyl, H <sup>+</sup>
k	H	H <sub>2</sub>	H	$\beta$ -(P-amino-phenyl)-ethyl, H <sup>+</sup>

	<u>R</u>	<u>R'</u>	<u>R''</u>
10a	Me	H <sub>2</sub>	$\beta$ -Furylcarbonyl
b*	Me	H <sub>2</sub>	$\beta$ -Furylcarbonyl
c	Me	H <sub>2</sub>	$\alpha$ -Methyl- $\beta$ -furylcarbonyl
d	Me	H <sub>2</sub>	$\alpha$ -Furylcarbonyl
e	Me	H <sub>2</sub>	Cyclopropylcarbonyl
f	Me	H <sub>2</sub>	$\gamma$ , $\gamma$ -Dimethylallyl
g	Me	H <sub>2</sub>	H
h	Et	=O	Cyclopropylcarbonyl
i	Me	=O	Cyclopropylcarbonyl
j**	$\emptyset$	H <sub>2</sub>	Propargyl
k	$\emptyset$	H <sub>2</sub>	$\beta$ -Hydroxyethyl

\*10b has Ac instead of H

\*\*10j has H instead of Me



	<u>R</u>	<u>R'</u>	
11a	Propyl	Cyclopropylcarbinyl	
b	Isobutyl	Cyclopropylcarbinyl	
c	Isopropyl	Allyl	
d	Propyl	Me	12

### Experimental

#### Instrument

<sup>13</sup>C-NMR spectra were determined at 22.63 MHz on a Bruker WH-90, Model B-NC 12 Fourier transform spectrometer interfaced with a Nicolet 1085 Fourier transform digital computer system.

#### Sample Preparation

An approximately one-hundred milligram sample was dissolved in 1 ml of 99.7% deuterium oxide solution in a 10-mm tube. The D<sub>2</sub>O deuterium resonance provided an internal lock signal but for greater accuracy the chemical shifts were referenced to internal dioxane at δ67.9.<sup>20</sup>

#### Instrumental Settings

Both broad-band decoupled and off-resonance spectra were run on each sample. Broad-band irradiation at 2500 Hz wide was provided by an incoherent 99.075 MHz source. Interograms were stored in 8K of computer memory (4K output data points in the transformed phase corrected real

spectrum), and chemical shifts were measured at 16K sweep time. The temperature range was 30-33°C, and the offset value was 6500 Hz. For off-resonance spectra the frequency setting on the decoupler was +1250 Hz, and the power value 25 watts.

#### Computer Commands<sup>21</sup>

The FT-74 program was used for all runs. After locking on the deuterium signal of the D<sub>2</sub>O in the sample, the following data acquisition commands were typed on the teletype:

SW Spectrum width set to 6024 Hz.

DW Dwell time set to 83 μ sec.

DE Delay time between pulses set at 10 sec to enhance signals due to quaternary carbons.

NS Number of scans set somewhere between 2000 and 7000.

CD Continuous display.

ZE Displayed memory segment cleared.

GO Data acquisition begun.

The scope was then turned off.

After data acquisition was complete (1-12 hours), the following commands were typed.

Q Caused end of data acquisition.

MO Caused a jump to location 7600, which allowed the DEMON/II monitor to be called in and started if a disk existed on the system.

FT Initiated a fast Fourier transform of the data currently displayed and replaced it with the frequency domain spectrum.

EP Allowed a know controlled zoom expansion of any region of the spectrum.

PK Routine phase corrected the last Fourier transformed block to the parameters which were used when the last phase correction was done on memory by the EP command.

AT Additive transfer used to improve resolution.

PL Caused a plot of the spectrum to be produced with each peak printed out on the teleprinter as it was plotted.

### Results and Discussion

The C-13 NMR chemical shift assignments for the 26 synthetic analgesics in Table B-5 were based on analysis of the noise-decoupled and off-resonance spectra. The multiplicities generated in the off-resonance spectra usually enabled distinction between methyl, methylene, methinyl, and quaternary carbon resonances. Sometimes triplets could not be distinguished from singlets, or doublets from quartets, because the outer lines were not above the noise level. Fortunately, comparisons of spectra of similar compounds eventually removed all ambiguities of this type.

The problem now was to assign the quartets in the off-resonance spectrum to methyl carbons in the molecule, triplets to methylenes, and so forth. This was aided in many cases by comparison of spectra of two similar substances which differed in that only one had a carbon of the type under consideration. Also very helpful were generalities on substituent effects<sup>20,22,23</sup>.

- (1) The substitution of a carbon (or a more electronegative atom or group) for a directly attached hydrogen produces a downfield shift (i.e., the more carbons which are  $\alpha$  to the carbon in question, the more downfield the C-13 shift [ $\alpha$  effect]).
- (2) The substitution of a carbon or other atom for a hydrogen attached to a carbon  $\alpha$  to the carbon in question also produces a downfield shift (i.e., the more substitution at the carbon  $\alpha$  to the carbon in question, the more downfield the C-13 shift [ $\beta$  effect]).
- (3) The hydrogens or other groups that are attached to carbons which are to the carbon in question produce an upfield shift ( $\gamma$  effect). The

$\alpha$  and  $\beta$  effects are presumably through-bond effects while the  $\gamma$  effect is a steric compression effect.

One difficult assignment involved the triplets at approximately  $\delta$  26 and 33 due to methylene carbons at C10 and C15 in compounds 2j-o and 9h-k. The latter triplet was much closer to the usual value for a bencylic methylene, but it was eventually realized that the p-hydroxyl group caused a large upfield shift<sup>24</sup>, and thus C10 absorbed at  $\delta$  26 and, by elimination, C15 absorbed at  $\delta$  33.

Another difficult problem was assigning the singlets at about  $\delta$  141 and 146 to quaternary carbons at C3 and C4. Our assignments are based on analogy to codeine(1b), for which the C3 and C4 absorptions were distinguished using  $T_1$  measurements.<sup>25</sup>

Comparison of the shifts measured in this study on protonated amines in D<sub>2</sub>O with shifts of free amines in DCCl<sub>3</sub> and d<sub>6</sub>-DMSO<sup>18,19</sup> shows rather small differences, and no cases which would require revision of assignments. In two cases (2f with 2l; 2g with 2m) the compounds are identical except for protonation. In these cases, the largest differences come in the sp<sup>2</sup> carbons of the N-allyl group of 2f and 2l: C19 is shifted downfield from  $\delta$  117.9 to  $\delta$  129.2 by protonation, and C18 is shifted upfield from  $\delta$  135.0 to 128.6. The shifts for the free allyl amine 2f are similar to these in allyl ethyl ether, whereas those in the protonated allyl amine 2l are much closer to those of ethyl acrylate<sup>26</sup>; this suggests considerable inductive polarization of the  $\pi$  electrons of the double bond in the protonated allyl amine 2l.

The current study complements the studies of Terui et al.<sup>18</sup> and Carroll et al.<sup>19</sup>. It should facilitate assignments of related compounds and may aid in the understanding of the mode of action of these analgesics.

APPENDIX A

TABLES FOR PART I:  
CRYSTAL STRUCTURE OF A NORDITERPENE DILACTONE

Table A-1. Fractional coordinates and estimated standard deviations.

Atom	<u>x/a</u>	<u>y/b</u>	<u>z/c</u>
Br	0.3479(1)	0.1755(5)	0.9892(1)
C1	0.4982(6)	0.1764(13)	0.8473(4)
C2	0.3939(6)	0.0456(13)	0.8859(4)
C3	0.2656(6)	0.0174(11)	0.8269(4)
C4	0.2844(6)	-0.0424(10)	0.7365(4)
C5	0.4040(5)	0.0746(11)	0.7039(4)
C6	0.4197(7)	-0.0573(13)	0.6258(4)
C7	0.5536(8)	-0.0303(17)	0.5920(4)
C8	0.6573(6)	0.0993(11)	0.6371(4)
C9	0.5370(5)	0.1889(12)	0.7239(3)
C10	0.5317(6)	0.0715(11)	0.7661(4)
C11	0.7281(6)	0.3353(11)	0.7582(4)
C12	0.8332(6)	0.4168(11)	0.7070(5)
O13	0.8616(5)	0.3059(9)	0.6420(3)
C14	0.8002(7)	0.0882(10)	0.6219(4)
C15	0.8253(7)	0.0389(17)	0.5351(6)
C16	0.8831(10)	-0.1530(21)	0.5158(6)
C17	0.0637(7)	-0.0970(19)	0.8769(6)
C18	0.1520(6)	0.0050(15)	0.6835(4)
C19	0.3170(6)	-0.2788(12)	0.7155(5)
C20	0.5909(6)	-0.1555(13)	0.7875(4)
C21	0.0064(12)	-0.2897(27)	0.9228(7)
O14	0.5690(5)	0.1950(12)	0.5686(3)
O15	0.3927(5)	-0.2799(9)	0.6494(3)
O16	0.8903(6)	0.5871(10)	0.7243(4)
O17	0.1868(5)	-0.1480(11)	0.8633(3)
O18	0.0057(6)	0.0722(17)	0.8581(5)
O19	0.2814(6)	-0.4470(10)	0.7448(5)
H1C1	0.572(8)	0.160(16)	0.893(5)
H2C1	0.446(8)	0.316(16)	0.829(5)
HC2	0.438(6)	-0.133(11)	0.893(4)
HC3	0.204(6)	0.145(13)	0.823(4)
HC5	0.387(8)	0.209(17)	0.680(5)
HC6	0.351(10)	-0.000(22)	0.582(6)
HC7	0.605(6)	-0.114(12)	0.531(4)
HC11	0.739(8)	0.379(14)	0.818(5)
HC14	0.824(7)	-0.027(14)	0.651(4)
HC15	0.823(8)	0.142(19)	0.487(4)
H1C16	0.885(9)	-0.124(18)	0.449(6)
H2C16	0.882(8)	-0.269(15)	0.561(5)
H1C18	0.154(6)	-0.042(12)	0.642(4)
H2C18	0.120(6)	0.195(11)	0.678(4)
H3C18	0.076(8)	-0.063(16)	0.697(5)
H1C20	0.515(6)	-0.272(13)	0.821(4)
H2C20	0.695(9)	-0.124(18)	0.811(6)

Table A-1. (continued)

Atom	<u>x/a</u>	<u>y/b</u>	<u>z/c</u>
H3C20	0.628(6)	-0.239(12)	0.741(4)
H1C21	0.030(9)	-0.460(20)	0.920(5)
H2C21	-0.102(9)	-0.299(20)	0.916(5)
H3C21	0.054(7)	-0.266(16)	0.975(5)

Table A-2. Thermal parameters of the form  $\exp(-[\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}kl] \times 10^4)$  with estimated standard deviations. Hydrogen atoms were given the thermal parameters of the atoms to which they were attached.

Atom	$\beta_{11}$	$\beta_{22}$	$\beta_{33}$	$\beta_{12}$	$\beta_{13}$	$\beta_{23}$
Br	108(1)	589(5)	37(0)	-48(2)	30(0)	-67(1)
C1	56(5)	23(17)	30(2)	3(10)	8(10)	-18(7)
C2	64(6)	260(21)	29(3)	-21(10)	19(3)	4(6)
C3	50(5)	164(16)	35(3)	16(8)	19(3)	3(6)
C4	75(6)	103(16)	27(3)	1(7)	1(3)	-2(5)
C5	57(5)	140(14)	21(2)	19(7)	7(3)	-2(5)
C6	102(7)	190(18)	25(3)	-7(10)	1(3)	11(6)
C7	96(7)	342(27)	27(3)	-3(12)	11(3)	-5(7)
C8	80(6)	200(16)	27(2)	30(8)	10(3)	-5(5)
C9	57(4)	157(14)	27(2)	4(8)	10(2)	2(5)
C10	53(5)	133(15)	28(3)	7(8)	12(3)	8(5)
C11	70(6)	175(15)	37(3)	-19(8)	15(3)	4(5)
C12	57(5)	180(17)	57(3)	-15(8)	20(4)	6(7)
O13	92(5)	235(13)	52(2)	-21(7)	30(3)	12(5)
C14	93(7)	164(15)	32(3)	-2(8)	19(3)	9(5)
C15	89(7)	452(31)	47(3)	27(13)	16(4)	26(9)
C16	150(10)	536(40)	49(4)	68(18)	19(5)	-76(11)
C17	68(7)	439(34)	53(4)	-31(14)	35(4)	17(10)
C18	59(6)	308(23)	36(3)	3(10)	2(3)	6(7)
C19	72(6)	126(18)	43(3)	8(9)	6(3)	-23(6)
C20	63(6)	189(17)	39(3)	14(9)	14(3)	31(6)
C21	192(14)	661(59)	57(5)	-203(28)	43(7)	53(15)
O14	87(5)	365(18)	30(2)	8(9)	8(2)	15(6)
O15	92(5)	205(14)	41(2)	-18(7)	21(2)	-26(5)
O16	124(6)	302(16)	72(3)	-34(9)	36(4)	-23(6)
O17	83(5)	263(15)	41(2)	-16(7)	17(3)	10(5)
O18	89(6)	561(33)	82(4)	63(13)	43(4)	7(10)
O19	109(6)	144(15)	82(4)	-11(7)	28(4)	-7(6)

Table A-3. Bond distances involving hydrogens.<sup>a</sup>

Atoms	Distance (Å)
C1 - H1	0.98
C1 - H2	1.03
C2 - H	1.17
C3 - H	0.99
C5 - H	0.92
C6 - H	0.99
C7 - H	1.16
C11 - H	0.98
C14 - H	0.86
C15 - H	0.99
C16 - H1	1.08
C16 - H2	1.02
C18 - H1	0.73
C18 - H2	1.20
C18 - H3	0.91
C20 - H1	1.21
C20 - H2	1.09
C20 - H3	1.00
C21 - H1	1.07
C21 - H2	1.08
C21 - H3	0.94

a. Estimated standard deviations are 0.07 - 0.09 Å.

Table A-4. Bond angles involving hydrogens.<sup>a</sup>

Atoms	Angle (°)
C2 - C1 - H1	98.2
C2 - C1 - H]	101.5
C10 - C1 - H1	111.8
C10 - C1 - H2	105.1
Br - C2 - H	115.0
C1 - C2 - H	105.2
C3 - C2 - H	103.6
C2 - C3 - H	115.7
C4 - C3 - H	105.1
C4 - C5 - H	116.6
C6 - C5 - H	99.0
C10 - C5 - H	112.8
C5 - C6 - H	105.7
C7 - C6 - H	106.6
O15 - C6 - H	112.4
C6 - C7 - H	133.2
C8 - C7 - H	106.3
O14 - C7 - H	97.2
C9 - C11 - H	125.0
C12 - C11 - H	115.4
C8 - C14 - H	99.5
O13 - C14 - H	122.2
C14 - C15 - H	127.7
C16 - C15 - H	110.2
C15 - C16 - H1	97.6
C15 - C16 - H2	113.9
C4 - C18 - H1	109.5
C4 - C18 - H2	115.6
C4 - C18 - H3	118.8
C10 - C20 - H1	112.6
C10 - C20 - H2	104.6
C10 - C20 - H3	117.2
C17 - C21 - H1	129.2
C17 - C21 - H2	114.3
C17 - C21 - H3	97.4

a. Estimated standard deviations are 2.0 - 3.0°.

Table A-5. Endocyclic torsion angles ( $^{\circ}$ ).

Ring	Bond	Angle	Ring	Bond	Angle
A	C1 - C2	-57.1	C	C8 - C9	30.5
	C2 - C3	44.5		C9 - C11	6.1
	C3 - C4	-38.2		C11 - C12	-19.9
	C4 - C5	45.5		C12 - O13	-5.6
	C5 - C10	-57.5		O13 - C14	40.8
	C10 - C1	63.0		C14 - C8	-51.4
B	C5 - C6	-41.3	$\gamma$ -Lactone	C4 - C5	37.9
	C6 - C7	4.6		C5 - C6	-38.2
	C7 - C8	6.0		C6 - O15	23.0
	C8 - C9	19.9		O15 - C19	2.3
	C9 - C10	-53.8		C19 - C4	-26.2
	C10 - C5	65.8			

Table A-6. Observed and calculated structure factors.

H	L	FO	FC	H	L	FO	FC	H	L	FO	FC	H	L	FO	FC	
***	K	=	0	***	-6	0	433	387	-3	10	180	170	1	4	17	21
-11	0	106	100	-6	1	323	307	-3	11	198	206	1	6	146	167	
-11	1	48	51	-6	2	310	314	-3	12	285	282	1	7	61	76	
-11	2	93	88	-6	3	102	85	-3	14	16	22	1	8	234	189	
-11	3	24	21	-6	4	232	220	-3	15	214	224	1	9	79	90	
-11	4	159	155	-6	5	245	242	-3	16	87	84	1	10	161	141	
-11	5	110	114	-6	6	517	515	-2	0	235	227	1	12	37	35	
-11	6	92	90	-6	7	347	341	-2	1	439	440	1	13	188	176	
-10	0	102	85	-6	8	345	344	-2	2	219	209	1	14	35	20	
-10	1	84	81	-6	9	29	27	-2	3	512	508	1	15	117	121	
-10	2	205	184	-6	10	224	205	-2	4	52	62	1	16	148	153	
-10	3	189	168	-6	11	81	96	-2	5	33	47	1	17	39	36	
-10	4	274	281	-6	12	51	55	-2	6	97	101	2	1	338	334	
-10	5	353	354	-6	13	209	227	-2	7	156	139	2	2	651	700	
-10	6	198	166	-6	14	133	137	-2	8	95	108	2	3	554	564	
-10	7	163	153	-6	15	21	10	-2	9	569	520	2	5	221	221	
-10	8	111	122	-6	16	35	41	-2	10	193	173	2	6	382	385	
-10	9	191	174	-5	0	236	225	-2	11	113	108	2	7	353	345	
-10	10	139	143	-5	1	197	202	-2	12	331	327	2	8	431	428	
-9	0	27	26	-5	2	324	302	-2	13	213	195	2	9	323	339	
-9	1	229	201	-5	3	121	113	-2	14	322	308	2	10	99	106	
-9	2	279	268	-5	4	677	660	-2	15	146	138	2	11	563	566	
-9	3	91	83	-5	5	316	290	-2	16	31	17	2	12	347	329	
-9	4	224	199	-5	6	346	355	-2	17	125	119	2	13	174	175	
-9	5	195	187	-5	7	140	137	-1	0	1050	922	2	14	135	125	
-9	6	16	34	-5	8	160	136	-1	.1	362	374	2	15	203	208	
-9	7	90	88	-5	9	181	172	-1	2	711	786	2	16	118	121	
-9	8	26	29	-5	10	702	675	-1	3	629	605	2	17	80	97	
-9	9	102	105	-5	11	112	97	-1	4	917	959	3	1	824	891	
-9	10	24	28	-5	12	140	132	-1	5	834	833	3	2	428	478	
-9	11	17	17	-5	13	364	351	-1	6	85	74	3	3	967	1073	
-9	12	60	50	-5	14	330	340	-1	7	573	595	3	4	1050	1143	
-8	0	87	89	-5	15	195	194	-1	8	688	701	3	5	76	75	
-8	1	87	85	-5	16	235	223	-1	9	520	533	3	6	286	332	
-8	2	57	51	-4	0	822	870	-1	10	567	581	3	7	433	444	
-8	3	164	158	-4	1	111	115	-1	11	367	366	3	8	236	255	
-8	4	37	33	-4	2	356	401	-1	12	395	385	3	9	325	323	
-8	5	154	160	-4	3	1169	1258	-1	13	337	316	3	10	307	333	
-8	6	355	350	-4	4	224	264	-1	14	287	277	3	11	532	535	
-8	7	202	206	-4	5	732	699	-1	15	58	52	3	12	159	155	
-8	8	153	151	-4	6	689	714	-1	16	199	200	3	13	16	14	
-8	9	74	76	-4	7	297	298	-1	17	200	223	3	14	231	252	
-8	10	215	201	-4	8	550	565	0	1	265	274	3	15	32	38	
-8	11	273	301	-4	9	481	489	0	2	489	500	3	16	48	45	
-8	12	273	279	-4	10	606	617	0	4	370	378	4	1	429	433	
-8	13	170	169	-4	11	569	558	0	5	197	216	4	2	522	572	
-7	0	59	55	-4	12	144	141	0	6	474	522	4	3	918	934	
-7	1	433	435	-4	13	178	168	0	7	833	856	4	4	457	481	
-7	2	691	699	-4	14	371	366	0	8	905	908	4	5	467	475	
-7	3	208	218	-4	15	232	237	0	9	215	253	4	6	352	390	
-7	4	304	293	-4	16	176	182	0	10	106	117	4	7	109	113	
-7	5	431	449	-4	17	178	191	0	11	415	431	4	8	21	32	
-7	6	371	360	-3	0	527	502	0	12	106	118	4	9	224	250	
-7	7	344	350	-3	2	411	410	0	13	148	161	4	10	150	154	
-7	8	500	528	-3	3	380	365	0	14	296	300	4	11	134	157	
-7	9	347	337	-3	4	259	284	0	15	38	38	4	12	214	195	
-7	10	375	364	-3	5	953	1035	0	16	101	102	4	13	122	129	
-7	12	122	123	-3	6	135	119	0	17	119	118	4	14	100	99	
-7	13	190	193	-3	7	430	398	1	1	109	104	4	15	56	56	
-7	14	116	124	-3	8	639	675	1	2	707	742	4	16	21	36	
-7	15	233	267	-3	9	202	195	1	3	548	579	5	1	85	85	

Table A-6. Observed and calculated structure factors (continued).

H	L	F0	FC	H	L	F0	FC	H	L	F0	FC	H	L	F0	FC
5	2	134	141	10	3	225	262	-7	13	153	170	-3	9	294	294
5	3	159	129	10	4	74	77	-7	14	151	152	-3	10	537	538
5	4	451	426	10	5	72	66	-6	0	197	187	-3	11	378	365
5	5	308	270	10	6	64	75	-6	1	414	404	-3	12	250	244
5	6	118	96	11	1	78	92	-6	2	252	228	-3	13	385	393
5	7	176	184	*** K = 1 ***				-6	3	271	269	-3	14	120	111
5	8	187	176	-11	0	91	80	-6	4	401	405	-3	15	267	254
5	9	122	117	-11	1	95	82	-6	5	216	209	-3	16	234	230
5	10	322	327	-11	2	120	106	-6	6	309	304	-3	17	174	181
5	11	102	91	-11	3	207	200	-6	7	410	388	-2	0	411	428
5	12	167	164	-11	4	156	150	-6	8	271	285	-2	1	900	1011
5	13	146	145	-11	5	99	83	-6	9	698	719	-2	2	923	908
5	14	56	57	-10	0	101	104	-6	10	297	294	-2	3	558	546
5	15	77	85	-10	1	48	51	-6	11	343	369	-2	4	684	685
6	1	551	548	-10	2	67	63	-6	12	316	320	-2	5	805	787
6	2	398	417	-10	3	48	50	-6	13	244	251	-2	6	1115	1151
6	3	576	593	-10	4	30	34	-6	14	221	216	-2	7	539	516
6	4	166	173	-10	5	112	125	-6	15	203	209	-2	8	316	334
6	5	72	77	-10	6	117	131	-5	0	450	472	-2	9	451	462
6	6	389	424	-10	7	105	93	-5	1	567	570	-2	10	338	337
6	7	251	260	-10	8	61	57	-5	2	720	724	-2	11	359	342
6	8	151	160	-10	9	103	97	-5	3	486	496	-2	12	301	293
6	9	146	153	-9	0	164	148	-5	4	621	628	-2	13	436	442
6	10	261	252	-9	1	146	147	-5	5	310	297	-2	14	159	160
6	11	125	116	-9	2	196	200	-5	6	524	541	-2	15	147	157
6	12	68	63	-9	3	215	208	-5	7	591	586	-2	16	223	226
6	13	158	164	-9	5	189	194	-5	8	114	101	-2	17	145	150
6	14	94	110	-9	6	393	399	-5	9	548	575	-1	0	671	631
7	1	467	490	-9	7	296	305	-5	10	419	414	-1	1	766	698
7	2	183	196	-9	8	159	157	-5	11	133	140	-1	2	529	508
7	3	268	272	-9	9	260	275	-5	12	292	292	-1	3	445	382
7	4	120	125	-9	10	278	280	-5	13	292	303	-1	4	680	703
7	5	107	113	-9	11	130	128	-5	14	145	140	-1	5	382	407
7	6	301	310	-9	12	244	248	-5	15	185	186	-1	6	777	756
7	7	129	127	-8	0	331	313	-5	16	179	192	-1	7	762	729
7	8	101	113	-8	1	203	170	-4	0	489	495	-1	8	329	281
7	9	38	46	-8	2	193	169	-4	1	262	241	-1	9	281	313
7	10	26	28	-8	3	371	368	-4	2	804	796	-1	10	324	344
7	11	61	60	-8	4	286	270	-4	3	206	210	-1	11	23	13
8	1	330	348	-8	5	416	395	-4	4	371	323	-1	12	108	117
8	2	164	153	-8	6	318	319	-4	5	266	256	-1	13	85	87
8	3	45	36	-8	7	222	236	-4	6	229	222	-1	14	145	145
8	4	99	120	-8	8	117	118	-4	7	163	168	-1	15	43	38
8	5	138	122	-8	9	195	169	-4	8	248	267	-1	16	150	151
8	6	46	42	-8	10	70	65	-4	9	257	277	-1	17	98	105
8	7	171	159	-8	11	165	172	-4	10	82	73	0	2	270	250
8	8	18	4	-8	12	211	228	-4	11	181	157	0	3	830	798
8	9	33	29	-8	13	104	102	-4	12	187	175	0	4	408	408
8	10	131	137	-7	0	152	157	-4	14	69	68	0	5	475	486
8	11	18	19	-7	1	158	123	-4	15	152	143	0	6	292	281
9	1	39	49	-7	2	137	116	-4	16	69	62	0	7	302	289
9	2	317	323	-7	3	253	245	-4	17	136	137	0	8	410	388
9	3	220	232	-7	4	116	111	-3	0	314	300	0	9	350	315
9	4	24	18	-7	5	104	102	-3	1	196	181	0	10	330	331
9	5	210	216	-7	6	68	77	-3	2	230	224	0	11	281	256
9	6	98	102	-7	7	175	175	-3	3	383	373	0	12	257	266
9	7	167	160	-7	8	96	78	-3	4	651	600	0	13	205	197
9	8	48	45	-7	9	81	81	-3	5	450	426	0	14	349	342
9	9	18	9	-7	10	26	35	-3	6	99	100	0	15	144	132
10	1	104	110	-7	11	152	144	-3	7	461	426	0	16	76	78
10	2	188	206	-7	12	68	57	-3	8	680	667	0	17	166	164

Table A-6. Observed and calculated structure factors (continued).

H	L	F0	FC	H	L	F0	FC	H	L	F0	FC	H	L	F0	FC
1	3	499	519	5	1	607	637	10	5	70	61	-6	8	329	351
1	4	760	762	5	2	368	415	10	6	60	62	-6	9	361	355
1	5	889	942	5	3	404	398	11	1	134	144	-6	10	159	157
1	6	524	525	5	4	520	530	*** K = 2 ***				-6	11	230	225
1	7	491	489	5	5	505	554	-10	0	83	71	-6	12	60	63
1	8	388	400	5	6	117	118	-10	1	163	159	-6	13	122	125
1	9	341	345	5	7	244	254	-10	2	241	250	-6	14	55	56
1	10	603	589	5	8	300	306	-10	3	104	93	-6	15	46	46
1	11	217	205	5	9	259	247	-10	4	241	238	-5	0	48	50
1	12	332	331	5	10	165	149	-10	5	187	175	-5	1	151	141
1	13	285	274	5	11	118	128	-10	6	74	62	-5	2	159	150
1	14	183	174	5	12	213	217	-10	7	103	106	-5	3	189	166
1	15	219	221	5	13	82	79	-10	8	244	249	-5	4	128	129
1	16	113	117	5	14	81	71	-9	0	247	228	-5	5	214	204
1	17	120	130	6	1	153	151	-9	1	176	157	-5	6	147	128
2	3	265	289	6	2	230	171	-9	2	46	41	-5	7	92	74
2	4	169	149	6	3	140	136	-9	3	92	84	-5	8	141	153
2	5	540	553	6	4	135	141	-9	4	226	196	-5	9	233	228
2	6	227	221	6	5	234	248	-9	5	195	184	-5	10	202	218
2	7	294	308	6	6	182	171	-9	6	43	30	-5	11	237	230
2	8	498	522	6	7	82	79	-9	7	169	180	-5	12	373	386
2	9	283	287	6	8	94	98	-9	8	78	69	-5	13	70	69
2	10	453	460	6	9	80	73	-9	9	48	41	-5	14	205	218
2	11	187	174	6	10	37	35	-9	10	28	24	-5	15	142	154
2	12	55	45	6	11	78	70	-9	11	72	55	-5	16	147	145
2	13	138	138	6	12	60	58	-8	0	197	185	-4	0	441	456
2	14	22	13	6	13	21	17	-8	1	163	150	-4	1	254	254
2	15	89	89	7	1	186	161	-8	2	51	46	-4	2	285	305
2	16	38	33	7	2	259	234	-8	3	150	138	-4	3	780	776
2	17	34	32	7	3	128	130	-8	4	88	101	-4	4	456	448
3	1	469	459	7	4	170	150	-8	5	122	116	-4	5	428	446
3	2	392	395	7	5	251	252	-8	6	134	141	-4	6	385	370
3	3	471	491	7	6	249	244	-8	7	335	348	-4	7	461	442
3	4	477	505	7	7	54	50	-8	8	274	280	-4	8	444	437
3	5	231	215	7	8	152	158	-8	9	127	139	-4	9	411	398
3	6	84	.88	7	9	206	199	-8	10	142	153	-4	10	332	333
3	7	92	94	7	10	42	32	-8	11	155	162	-4	11	415	407
3	8	131	120	7	11	136	141	-8	12	121	131	-4	12	293	306
3	9	240	239	7	12	142	138	-7	0	413	393	-4	13	147	139
3	10	166	161	8	1	307	308	-7	1	358	374	-4	14	311	303
3	11	247	249	8	2	450	461	-7	2	108	100	-4	15	182	189
3	12	353	337	8	3	179	206	-7	3	318	321	-4	16	182	178
3	13	91	104	8	4	256	252	-7	4	359	367	-3	0	774	773
3	14	97	107	8	5	121	108	-7	5	439	447	-3	1	488	525
3	15	86	79	8	6	84	89	-7	6	268	249	-3	2	440	406
3	16	114	122	8	7	155	128	-7	7	317	320	-3	3	978	972
4	1	109	102	8	8	188	192	-7	8	486	491	-3	4	529	519
4	2	473	460	8	9	142	151	-7	9	45	46	-3	5	337	332
4	3	413	385	8	10	30	25	-7	10	134	137	-3	6	375	349
4	4	505	493	8	11	96	93	-7	11	292	301	-3	7	231	233
4	5	626	620	9	1	144	141	-7	12	215	224	-3	8	435	428
4	6	312	337	9	2	243	258	-7	13	222	218	-3	9	211	222
4	7	281	304	9	3	37	31	-7	14	160	160	-3	10	327	315
4	8	292	320	9	4	80	66	-6	0	389	382	-3	11	259	262
4	9	240	235	9	5	90	93	-6	1	340	347	-3	12	170	168
4	10	159	134	9	7	104	107	-6	2	272	283	-3	13	122	101
4	11	284	268	9	8	61	66	-6	3	70	139	-3	14	253	251
4	12	305	297	10	1	148	153	-6	4	183	189	-3	15	44	39
4	13	127	124	10	2	81	99	-6	5	238	246	-3	16	87	80
4	14	128	133	10	3	36	28	-6	6	180	203	-2	0	171	153
4	15	90	96	10	4	129	128	-6	7	98	84	-2	1	452	399

Table A-6. Observed and calculated structure factors (continued).

H	L	F0	FC	H	L	F0	FC	H	L	F0	FC	H	L	F0	FC
-2	2	335	312	1	10	172	180	5	9	115	114	-9	4	192	190
-2	3	444	393	1	11	157	137	5	10	148	151	-9	5	223	211
-2	4	284	267	1	12	51	52	5	11	77	77	-9	6	84	93
-2	5	365	305	1	13	134	136	5	12	73	71	-9	7	146	138
-2	6	463	414	1	14	63	68	5	13	137	141	-9	8	76	92
-2	7	251	243	1	15	168	169	5	14	125	125	-9	9	176	189
-2	8	237	239	1	16	117	128	6	1	446	448	-8	0	224	225
-2	9	132	125	2	1	145	137	6	2	214	229	-8	1	256	238
-2	10	97	88	2	2	659	606	6	3	197	199	-8	2	245	234
-2	11	214	204	2	3	474	449	6	4	224	215	-8	3	248	244
-2	12	196	210	2	4	344	334	6	5	350	348	-8	4	145	158
-2	13	183	191	2	5	310	320	6	6	243	248	-8	5	94	82
-2	14	133	119	2	6	427	397	6	7	233	260	-8	6	201	203
-2	15	174	183	2	7	367	375	6	8	229	225	-8	7	147	144
-2	16	145	139	2	8	300	283	6	9	66	63	-8	9	192	184
-2	17	72	76	2	9	284	269	6	10	144	143	-8	10	239	240
-1	0	750	703	2	10	479	474	6	11	105	105	-8	11	67	67
-1	1	341	290	2	11	338	312	6	12	114	116	-7	0	340	338
-1	2	320	275	2	12	44	48	6	13	125	121	-7	1	157	129
-1	3	445	404	2	13	195	205	7	1	212	217	-7	2	256	229
-1	4	507	480	2	14	133	131	7	2	152	140	-7	3	95	98
-1	5	262	281	2	15	160	171	7	3	315	301	-7	4	112	111
-1	6	699	683	2	16	139	139	7	4	180	184	-7	5	151	160
-1	7	833	800	3	1	360	356	7	5	165	166	-7	6	188	201
-1	8	287	256	3	2	454	421	7	6	213	208	-7	7	149	151
-1	9	355	353	3	3	672	674	7	7	152	168	-7	8	64	60
-1	10	251	255	3	4	510	504	7	8	85	76	-7	9	104	107
-1	11	361	356	3	5	185	194	7	9	113	114	-7	10	109	93
-1	12	235	225	3	6	515	514	7	10	107	94	-7	11	62	61
-1	13	253	245	3	7	442	446	7	11	123	117	-7	12	85	94
-1	14	328	313	3	8	257	254	8	1	458	492	-6	0	62	69
-1	15	238	228	3	9	268	265	8	2	78	72	-6	1	295	285
-1	16	129	125	3	10	278	270	8	3	139	150	-6	2	394	384
-1	17	161	153	3	11	320	299	8	4	67	64	-6	3	58	50
0	0	851	825	3	12	71	68	8	5	63	64	-6	4	168	162
0	1	671	591	3	13	217	223	8	6	76	68	-6	5	32	28
0	2	747	695	3	14	160	143	8	7	82	82	-6	6	318	320
0	3	856	798	3	15	157	152	8	8	18	21	-6	7	275	279
0	4	565	529	4	1	269	261	8	9	76	76	-6	8	228	240
0	5	482	462	4	2	121	128	8	10	85	83	-6	9	244	244
0	6	455	440	4	3	342	322	9	1	101	90	-6	10	218	226
0	7	522	517	4	4	487	483	9	2	74	84	-6	11	117	125
0	8	237	227	4	5	262	235	9	3	222	233	-6	12	152	162
0	9	312	305	4	6	71	67	9	4	109	119	-6	13	220	228
0	10	167	176	4	7	297	295	9	5	30	32	-6	14	135	148
0	11	381	377	4	8	121	113	9	6	81	85	-5	0	256	259
0	12	245	231	4	9	66	64	9	7	84	86	-5	1	342	316
0	13	186	179	4	10	178	176	10	1	86	82	-5	2	388	380
0	14	281	269	4	11	194	183	10	2	49	58	-5	3	323	334
0	15	51	40	4	12	93	84	10	3	139	143	-5	4	275	265
0	16	96	86	4	13	56	51	10	4	132	134	-5	5	281	267
0	17	103	91	4	14	69	78	***	K = 3 ***	***	***	-5	6	295	303
1	1	548	459	4	15	71	66	-10	0	86	80	-5	7	257	233
1	2	193	168	5	1	166	162	-10	1	52	58	-5	8	118	110
1	3	590	571	5	2	301	315	-10	2	96	90	-5	9	280	274
1	4	100	87	5	3	57	67	-10	3	58	52	-5	10	106	103
1	5	198	157	5	4	138	138	-10	4	143	132	-5	11	259	262
1	6	238	205	5	5	147	145	-9	0	122	110	-5	12	100	104
1	7	113	109	5	6	171	172	-9	1	95	94	-5	13	204	178
1	8	255	257	5	7	216	210	-9	2	108	99	-5	14	153	159
1	9	270	254	5	8	153	148	-9	3	150	145	-4	0	162	168

Table A-6. Observed and calculated structure factors (continued).

H	L	F0	FC	H	L	F0	FC	H	L	F0	FC	H	L	F0	FC
-4	1	122	141	-1	13	201	168	3	12	53	57	9	3	102	100
-4	2	36	33	-1	14	143	142	3	13	68	85	9	4	56	45
-4	3	324	315	-1	15	55	55	3	14	128	142	9	5	95	84
-4	4	307	308	-1	16	101	104	4	1	198	198	10	1	59	65
-4	5	50	56	0	1	167	154	4	2	377	361	*** K = 4 ***			
-4	6	123	140	0	2	366	335	4	3	154	148	-9	0	60	60
-4	7	39	38	0	3	52	60	4	4	124	132	-9	1	43	46
-4	8	99	118	0	4	151	126	4	5	422	438	-9	2	52	60
-4	9	231	211	0	5	335	312	4	6	183	192	-9	3	22	21
-4	10	133	122	0	6	79	72	4	7	110	113	-9	4	72	79
-4	11	77	77	0	7	131	129	4	8	169	164	-8	0	48	53
-4	12	52	48	0	8	316	311	4	9	259	268	-8	1	100	109
-4	13	189	189	0	9	200	201	4	10	126	125	-8	2	86	80
-4	14	96	90	0	10	234	244	4	11	112	111	-8	4	143	125
-4	15	117	121	0	11	146	157	4	12	143	143	-8	5	73	80
-3	0	380	372	0	12	167	179	4	13	149	154	-8	6	48	39
-3	1	195	196	0	13	151	148	4	14	75	77	-8	7	62	65
-3	2	209	193	0	14	112	101	5	1	395	409	-8	8	99	111
-3	3	332	308	0	15	184	191	5	2	408	405	-7	0	216	206
-3	4	193	202	0	16	200	215	5	3	75	72	-7	1	200	198
-3	5	524	494	1	1	561	533	5	4	182	171	-7	2	135	135
-3	6	434	422	1	2	434	382	5	5	356	367	-7	3	117	108
-3	7	235	263	1	3	393	378	5	6	289	281	-7	4	218	223
-3	8	68	61	1	4	247	254	5	7	132	125	-7	5	109	115
-3	9	124	132	1	5	464	468	5	8	194	182	-7	6	152	155
-3	10	220	219	1	6	231	230	5	9	135	122	-7	7	135	128
-3	11	272	279	1	7	371	360	5	10	111	96	-7	8	133	145
-3	12	265	266	1	8	503	486	5	11	152	136	-7	9	106	101
-3	13	290	290	1	9	298	282	5	12	104	99	-7	10	55	49
-3	14	124	120	1	10	156	153	5	13	48	41	-6	0	162	144
-3	15	131	135	1	11	74	67	6	1	137	121	-6	1	312	316
-2	0	145	130	1	12	223	217	6	2	101	70	-6	2	63	62
-2	1	351	319	1	13	195	196	6	3	34	38	-6	3	101	108
-2	2	614	562	1	14	192	188	6	4	164	170	-6	4	348	345
-2	3	486	452	1	15	182	171	6	5	143	132	-6	5	47	48
-2	4	742	702	2	1	508	478	6	6	110	105	-6	6	191	197
-2	5	456	437	2	2	548	498	6	7	166	160	-6	7	117	122
-2	6	366	352	2	3	354	310	6	8	117	129	-6	8	51	50
-2	7	251	230	2	4	382	353	6	9	96	104	-6	9	46	40
-2	8	260	261	2	5	342	303	6	10	77	73	-6	10	101	99
-2	9	239	236	2	6	196	186	6	11	40	38	-6	11	101	103
-2	10	371	359	2	7	292	274	7	1	262	261	-6	12	96	101
-2	11	172	170	2	8	187	175	7	2	157	155	-5	0	59	54
-2	12	306	297	2	9	212	206	7	3	72	75	-5	1	130	140
-2	13	259	242	2	10	282	279	7	4	108	117	-5	2	128	136
-2	14	61	49	2	11	86	89	7	5	18	9	-5	3	294	278
-2	15	156	144	2	12	229	205	7	6	93	97	-5	4	110	113
-2	16	160	159	2	13	196	177	7	7	124	126	-5	5	64	70
-1	0	282	280	2	14	67	57	7	8	187	198	-5	6	51	55
-1	1	389	338	2	15	74	79	7	9	136	135	-5	7	66	69
-1	2	388	343	3	1	260	242	7	10	55	62	-5	8	68	68
-1	3	325	286	3	2	457	401	8	1	107	120	-5	9	88	112
-1	4	368	300	3	3	171	138	8	2	90	89	-5	10	23	5
-1	5	237	214	3	4	173	184	8	3	91	97	-5	11	122	132
-1	6	235	210	3	5	215	215	8	4	87	94	-5	12	214	240
-1	7	132	154	3	6	40	49	8	5	196	197	-5	13	72	74
-1	8	312	283	3	7	146	160	8	6	119	118	-4	0	176	162
-1	9	229	238	3	8	100	96	8	7	89	92	-4	1	197	193
-1	10	106	109	3	9	110	113	8	8	81	83	-4	2	111	121
-1	11	80	57	3	10	109	101	9	1	17	14	-4	3	194	195
-1	12	66	60	3	11	149	159	9	2	112	111	-4	4	345	350

Table A-6. Observed and calculated structure factors (continued).

H	L	FO	FC	H	L	FO	FC	H	L	FO	FC	H	L	FO	FC
-4	5	274	280	0	7	330	310	5	2	152	144	-5	10	119	118
-4	6	135	127	0	8	198	191	5	3	71	85	-4	0	94	95
-4	7	187	196	0	9	110	102	5	4	169	164	-4	1	116	124
-4	8	342	343	0	10	193	172	5	5	70	45	-4	2	79	84
-4	9	117	112	0	11	153	154	5	6	128	142	-4	3	115	117
-4	10	190	193	0	12	147	134	5	7	213	241	-4	4	33	34
-4	11	158	155	0	13	102	111	5	8	53	60	-4	5	116	109
-4	12	214	212	0	14	184	168	5	9	43	53	-4	6	113	113
-4	13	100	100	1	1	361	360	5	10	108	123	-4	7	149	148
-3	0	270	283	1	2	386	354	5	11	53	58	-4	8	90	102
-3	1	65	67	1	3	151	120	6	1	129	155	-4	9	58	47
-3	2	190	197	1	4	249	234	6	2	116	111	-4	10	73	82
-3	3	352	328	1	5	195	178	6	3	231	238	-4	11	58	71
-3	4	225	222	1	6	176	178	6	4	179	197	-3	0	165	163
-3	5	267	247	1	7	157	132	6	5	118	109	-3	1	144	143
-3	6	114	107	1	8	176	156	6	6	159	162	-3	2	123	116
-3	7	46	42	1	9	254	287	6	7	208	216	-3	3	125	121
-3	8	304	310	1	10	55	59	6	8	106	105	-3	4	35	25
-3	9	187	182	1	11	102	88	6	9	18	10	-3	5	260	263
-3	10	150	140	1	12	108	98	6	10	138	142	-3	6	191	212
-3	11	204	194	1	13	139	153	7	1	157	153	-3	7	175	178
-3	12	100	97	1	14	78	79	7	2	60	49	-3	8	56	65
-3	13	56	48	2	1	183	166	7	3	48	31	-3	9	187	200
-3	14	48	30	2	2	63	69	7	4	112	114	-3	10	70	83
-2	0	85	83	2	3	76	87	7	5	73	74	-3	11	41	43
-2	1	225	217	2	4	272	279	7	6	151	139	-2	0	123	138
-2	2	201	200	2	5	136	124	7	7	96	95	-2	1	278	280
-2	3	215	203	2	6	282	281	7	8	82	78	-2	2	170	197
-2	4	226	210	2	7	165	167	8	1	62	65	-2	3	134	123
-2	5	24	24	2	8	106	112	8	2	22	33	-2	4	215	197
-2	6	176	191	2	9	195	206	8	3	87	85	-2	5	334	309
-2	7	39	50	2	10	216	217	8	4	113	112	-2	6	72	73
-2	8	24	35	2	11	73	77	8	5	26	31	-2	7	161	165
-2	9	192	203	2	12	64	70	9	1	60	66	-2	8	126	110
-2	10	62	66	2	13	85	85	***	K = 5 ***	***	***	-2	9	133	127
-2	11	23	41	3	1	193	202	-7	0	49	52	-2	10	62	63
-2	12	123	124	3	2	221	217	-7	1	48	49	-2	11	73	67
-2	13	87	95	3	3	254	236	-7	2	110	110	-2	12	92	90
-2	14	102	115	3	4	252	259	-7	3	107	106	-1	0	153	153
-1	0	345	317	3	5	148	151	-7	4	84	89	-1	1	117	118
-1	1	196	177	3	6	271	267	-7	5	21	20	-1	2	90	77
-1	2	185	164	3	7	120	125	-7	6	15	8	-1	3	121	107
-1	3	324	298	3	8	122	124	-6	0	42	49	-1	4	238	199
-1	4	32	42	3	9	228	227	-6	1	21	15	-1	5	250	222
-1	5	200	202	3	10	74	73	-6	2	178	170	-1	6	111	100
-1	6	437	443	3	11	137	126	-6	3	58	51	-1	7	82	75
-1	7	257	249	3	12	85	80	-6	4	97	100	-1	8	44	30
-1	8	91	91	3	13	108	103	-6	5	133	128	-1	9	48	51
-1	9	209	216	4	1	167	157	-6	6	107	101	-1	10	138	135
-1	10	100	99	4	2	55	49	-6	7	123	132	-1	11	137	134
-1	11	218	214	4	3	106	96	-6	8	55	63	-1	12	49	40
-1	12	182	178	4	4	164	149	-5	0	89	82	0	1	80	81
-1	13	117	111	4	5	129	131	-5	1	207	200	0	2	221	189
-1	14	169	166	4	6	208	190	-5	2	248	243	0	3	99	94
0	0	97	95	4	7	99	81	-5	3	137	153	0	4	94	81
0	1	241	213	4	8	129	135	-5	4	92	77	0	5	189	203
0	2	433	381	4	9	114	103	-5	5	107	109	0	6	128	117
0	3	376	347	4	10	81	92	-5	6	112	122	0	7	186	179
0	4	153	145	4	11	69	71	-5	7	35	21	0	8	212	221
0	5	189	175	4	12	78	74	-5	8	100	96	0	9	98	85
0	6	207	192	5	1	163	149	-5	9	142	138	0	10	112	119

Table A-6. Observed and calculated structure factors (continued).

H	L	FO	FC	H	L	FO	FC	H	L	FO	FC
0	11	107	109	***	K	=	6 ***	3	2	53	46
0	12	92	104	-5	0	35	32	3	3	92	104
1	1	53	47	-5	1	61	60	3	4	162	166
1	2	204	204	-5	2	54	55	3	5	127	142
1	3	297	290	-5	3	27	36	3	6	36	33
1	4	203	176	-5	4	92	93	4	1	65	76
1	5	190	194	-4	0	20	22	4	2	73	80
1	6	138	148	-4	2	42	38	4	3	20	24
1	7	89	83	-4	3	79	74	4	4	94	91
1	8	233	236	-4	4	50	53	4	5	92	103
1	9	121	115	-4	5	48	44	5	1	41	48
1	10	44	43	-4	6	58	63	5	2	35	36
1	11	90	96	-3	0	70	80				
1	12	110	101	-3	1	84	81				
2	1	152	153	-3	2	29	12				
2	2	28	23	-3	3	129	130				
2	3	291	301	-3	4	116	119				
2	4	71	73	-3	5	28	33				
2	5	54	50	-3	6	20	29				
2	6	88	94	-3	7	70	65				
2	7	101	96	-2	0	46	48				
2	8	178	162	-2	1	174	186				
2	9	66	57	-2	2	78	77				
2	11	94	95	-2	3	93	95				
3	1	129	129	-2	4	95	97				
3	2	115	104	-2	5	43	38				
3	3	72	75	-2	6	59	60				
3	4	79	72	-2	7	19	25				
3	5	70	70	-2	8	90	83				
3	6	167	174	-1	0	80	90				
3	7	49	71	-1	1	109	110				
3	8	45	40	-1	2	85	79				
3	9	35	46	-1	3	58	66				
3	10	39	38	-1	4	88	91				
4	1	20	17	-1	5	84	72				
4	2	99	116	-1	6	37	42				
4	3	69	77	-1	7	140	136				
4	4	81	99	-1	8	47	55				
4	5	248	254	0	0	152	173				
4	6	66	73	0	1	138	136				
4	7	156	165	0	2	121	108				
4	8	45	49	0	3	107	106				
4	9	45	51	0	4	73	86				
5	1	115	124	0	5	130	116				
5	2	148	155	0	6	104	90				
5	3	144	149	0	7	97	97				
5	4	92	86	0	8	29	31				
5	5	154	147	1	1	109	110				
5	6	183	190	1	2	61	58				
5	7	109	107	1	3	71	84				
5	8	39	45	1	4	49	55				
6	1	37	31	1	5	123	117				
6	2	95	86	1	7	51	51				
6	3	72	69	1	8	38	46				
6	4	67	81	2	1	76	80				
6	5	141	131	2	2	19	34				
6	6	81	88	2	3	57	54				
7	1	34	26	2	4	63	65				
7	2	40	48	2	5	27	24				
7	3	57	67	2	6	76	85				
7	4	63	74	2	7	65	71				

APPENDIX B

TABLES FOR PART II:  
CMR SPECTRA OF ANALGESICS

Table B-1.  $^{13}\text{C}$  Chemical shift data on morphine alkaloids examined,  $\delta_{\text{C}}$  in  $\text{CDCl}_3$ .<sup>a,18</sup>

Carbon No.	Compound																
	1b	1f	1i	2a	2c	2d	3	4	7	8	9a	9b	9c	9d	9e	9f	9g
1	128.3	128.2	129.0	128.5	128.4	128.2	128.3	117.9	119.3	119.7	119.5	118.5	118.7	119.5	119.1	118.3	
2	111.0 <sup>b</sup>	110.9 <sup>b</sup>	111.7	110.7 <sup>b</sup>	111.4 <sup>b</sup>	111.2 <sup>b</sup>	110.0 <sup>b</sup>	110.9 <sup>b</sup>	109.1	112.8	114.7	115.1	113.2	113.4	115.3	112.9	113.6
3	158.0	158.0	157.7	158.2	158.1	158.0	158.2 <sup>b</sup>	158.0	145.2 <sup>b</sup>	142.0	142.3	142.5	143.5	141.3	142.7	142.7	142.9
4	110.6 <sup>b</sup>	110.6 <sup>b</sup>	111.7	111.2 <sup>b</sup>	112.2 <sup>b</sup>	112.2 <sup>b</sup>	112.5 <sup>b</sup>	112.0 <sup>b</sup>	144.8 <sup>b</sup>	146.2	144.6	144.2	144.1	146.4	145.4	144.6	145.0
5	37.1	36.6	41.3	45.6	51.9	51.5	45.0	49.5	49.1	91.3	88.0	87.0	89.6	90.5	91.2	89.0	88.5
6	22.2	22.3	67.6	66.4	192.9	192.8	191.8	197.2	193.4	66.4	194.1	194.2	29.4	66.9	207.0	152.3	152.1
7	26.8 <sup>c</sup>	26.3 <sup>c</sup>	33.2	35.8	41.3	41.9	37.4 <sup>c</sup>	130.9	152.3	133.2	132.2	134.3	21.7	26.8	40.1	95.8	98.0
8	26.7 <sup>c</sup>	26.6 <sup>c</sup>	21.2	25.5	27.1	26.7	31.7	149.4	115.3	128.1	149.1	147.5	25.1	19.3	25.6	111.3	23.6
9	51.3	57.9	57.7	57.4	50.2	57.0	62.1	56.1	56.6	58.7	58.9	64.1	59.9	59.6	59.2	60.7	58.9
10	33.8	23.4	23.4	23.3	33.4	23.1	23.8	23.8	24.4	20.4	20.4	22.5	20.2	20.1	20.1	29.5	20.3
11	130.1	129.7	129.0	128.8	128.4	128.2	127.0	128.2	130.3	127.0	126.1	125.0	127.2	126.8	126.4	127.6	127.0
12	141.7	141.5	141.5	141.0	138.6	138.6	140.3	138.8	122.7	130.9	129.0	130.3	130.1	127.4	133.1	129.1	
13	38.4	37.2	35.6	37.6	41.9	40.9	45.0	39.9	40.5	43.1	46.6	42.5	42.1	46.8	46.0	42.5	
14	46.2	45.4	45.2	44.1	44.4	43.9	69.0	45.6	45.7	40.7	41.4	67.7	43.4	39.7	42.5	132.3	39.9
15	42.9	42.1	42.8	41.7	42.5	40.9 <sup>c</sup>	36.8 <sup>c</sup>	39.9	35.8	35.8	33.9	29.5	35.7	37.1	35.5	37.0	35.8
16	39.2	47.2	46.8	46.6	38.0	46.0	46.4	46.4	47.1	46.4	46.7	45.1	47.7	46.6	46.8	46.0	46.4
NMe	--	42.7	42.6	42.6	--	42.7	42.7	42.7	42.5	43.0	42.9	42.5	43.0	42.7	42.7	42.3	43.0
3-OMe	55.2	54.9	55.0	55.2	55.1	55.0	55.1	55.0	55.8	56.7	56.7	56.8	56.5	56.4	57.0	56.2	56.4
OMe	--	--	--	--	--	--	--	--	54.6	--	--	--	--	--	54.7	54.2	

a.  $^{13}\text{C}$  FT NMR spectra were measured with a Varian NV-14 FT NMR spectrometer at 15.09 MHz in 8-mm tubes at ordinary probe temperature ( $30^\circ$ ). Samples were dissolved in  $\text{CDCl}_3$  containing TMS as an internal reference ( $\delta_0$ ); concentrations were about 1 mmole/cm<sup>3</sup>. PND FT NMR measurement conditions were almost the same for all compounds except for the number of transients for a few samples of small quantities; spectral width: 3319 Hz, pulse width: 10  $\mu\text{sec}$  (flipping angles of about  $15^\circ$ ), acquisition time: 0.6 sec, number of data points: 4077, and number of transients: 3000.

b,c. These assignments may be interchanged in each column.

Table B-2. Carbon-13 NMR chemical shifts of morphine systems.<sup>a,b,19</sup>

Identification of Carbon <sup>c</sup>	1a <sup>d</sup>	1b <sup>e</sup>	1c <sup>e</sup>	1d <sup>e</sup>	2b <sup>d</sup>	2c <sup>e</sup>	2d <sup>e</sup>	4 <sup>e</sup>
1	118.60	119.39	119.10	119.34	118.08	118.75	119.73	118.85
2	116.36	112.81	121.63	117.20	116.77	112.90	114.63	112.26
3	138.45	142.12	132.02	138.41	138.03	141.18	142.82	142.45
4	146.30	146.17	149.14	145.53	146.08	145.97	144.75	144.40
5	91.49	91.15	88.47	87.88	90.04	90.22	90.95	88.81
6	66.38	66.18	67.89	68.27	66.19	66.86	207.26	152.15
7	133.43	133.39	129.24	129.78	25.71 <sup>f</sup>	26.72 <sup>b</sup>	39.21	95.59
8	128.50	127.83	128.21	128.02	19.61 <sup>f</sup>	19.70 <sup>b</sup>	25.21	111.19
9	58.09	58.76	58.67 <sup>f</sup>	58.62	59.02 <sup>f</sup>	59.40 <sup>b</sup>	59.40	60.47
10	20.20	20.38	20.43 <sup>f</sup>	20.33	19.61 <sup>f</sup>	18.92 <sup>b</sup>	19.70	29.17
11	125.53	126.71	131.48	125.09	125.30	126.70	125.02	127.33
12	131.04	131.10	131.24	129.29	130.13	130.02	126.12	131.96 <sup>f</sup>
13	42.97	42.90	42.57	42.62	42.10	41.88	45.60	45.70 <sup>f</sup>
14	40.63	40.33	40.38	39.94	38.24	40.08	40.33	132.94
15	35.56	35.40	34.92	34.71	37.27	37.06	34.61	36.73 <sup>b</sup>
16	46.05	46.28	46.28	46.33	46.10	46.48	46.83	45.70 <sup>b</sup>
N-CH <sub>3</sub>	42.83	42.76	42.77	42.38	42.83	42.66	42.30	42.09
O-CH <sub>3</sub>			56.18			56.08	56.58	56.09
O-CH <sub>3</sub>								54.58
CH <sub>3</sub> CO			20.43					
CH <sub>3</sub> CO			168.16 <sup>f</sup>					
CH <sub>3</sub> CO			20.43 <sup>f</sup>	20.67				
CH <sub>3</sub> CO			170.20	170.36				

- a. Chemical shifts are in parts per million relative to tetramethylsilane.  
 b. Signals in any one column may be reversed.  
 c. Numbering of carbons is shown in Chart 1.  
 d. In dimethylsulfoxide-d<sub>6</sub> solution.  
 e. In chloroform-d solution.  
 f. These resonances were twice as intense as other similar carbons.

Table B-3. Carbon-13 NMR chemical shifts of 14-hydroxymorphine systems.<sup>a,b,19</sup>

Identification of Carbon <sup>c</sup>	1e <sup>d</sup>	1f <sup>e</sup>	1g <sup>e</sup>	1h <sup>e</sup>	2e <sup>e</sup>	2f <sup>e</sup>	2g <sup>e</sup>	2i <sup>e</sup>	2h <sup>e</sup>
1	119.54	119.33	119.50	119.38	119.21	119.65 <sup>f</sup>	119.70	118.94	118.89
2	117.45	114.80	122.97	114.86	114.63	117.89 <sup>f</sup>	117.92	117.63	117.53
3	139.15	142.47	132.13	144.23	142.65	138.81	138.77	137.37	139.81
4	142.91	144.06	147.35	146.41	144.65	143.45	143.41	145.57 <sup>h</sup>	142.30 <sup>i</sup>
5	86.57	86.89	87.66	87.01	90.13	90.21	90.36 <sup>g</sup>	90.51 <sup>h</sup>	95.78 <sup>i</sup>
6	194.80	194.00	192.29	193.05	208.21	209.67	209.86	66.77	72.62 <sup>j</sup>
7	132.81	134.37	134.07	133.84	35.90 <sup>b</sup>	35.97	36.02 <sup>g</sup>	22.97 <sup>b,h</sup>	26.00 <sup>i</sup>
8	150.61	147.29	145.94	145.94	31.20 <sup>b</sup>	31.04	31.20	28.64	30.53
9	62.92	63.93	58.05	57.93	64.34	62.00	61.87	61.94 <sup>b</sup>	62.14
10	22.05	22.22	22.74	22.28	21.69	22.57	22.51	22.69 <sup>b</sup>	22.63
11	124.08	124.79	130.48	125.61	124.67	123.76	123.85	125.23	123.72
12	130.86	130.25	131.07	129.90	129.14	128.82	128.84	130.84	131.38
13	46.38	46.42	46.77	46.65	49.94	50.78	50.88	47.26	47.26
14	67.70	67.57	76.56	76.73	70.10 <sup>b</sup>	70.53	70.27 <sup>j</sup>	69.89	70.38
15	28.92	29.74	28.73	28.86	30.26 <sup>b</sup>	30.27	30.44 <sup>j</sup>	33.22	29.56
16	45.12	44.95	45.13	45.24	45.01	43.20	43.48 <sup>j</sup>	43.07	43.90
N-CH <sub>3</sub>	42.33	42.37	42.54	42.54	42.48				
O-CH <sub>3</sub>		56.64		56.58	56.58				
14 CH <sub>3</sub> CO			169.91	169.79					
14 CH <sub>3</sub> CO			21.50 <sup>b</sup>	21.45					
3 CH <sub>3</sub> CO			168.03 <sup>b</sup>						
3 CH <sub>3</sub> CO			20.56 <sup>b</sup>						
N-CH <sub>2</sub>						57.48	59.05	59.40	59.06
CH <sub>2</sub> =CH						117.89 <sup>f</sup>			

Table B-3. (continued)

Identification of Carbon <sup>c</sup>	1e <sup>d</sup>	1f <sup>e</sup>	1g <sup>e</sup>	1h <sup>e</sup>	2e <sup>e</sup>	2f <sup>e</sup>	2g <sup>e</sup>	2i <sup>e</sup>	2h <sup>e</sup>
$\text{CH}_2=\text{CH}$					134.98				
$\begin{array}{c} \text{CH} \\   \\ \text{CH}_2 \\   \\ \text{CH}_2 \end{array} > \text{CH}-$						9.23	9.18	9.23	
$\begin{array}{c} \text{CH} \\   \\ \text{CH}_2 \\   \\ \text{CH}_2 \end{array} > \text{CH}-$					3.88	3.82	3.65	3.62	3.91 <sup>f</sup>

a,b,c,d,e,f. See footnotes to Table B-2.

g. The  $^{13}\text{C}$ -nmr spectrum of a sample of naltrexone which was partially deuterated in the 5 and 7 positions showed reduced intensities for the 90.36 and 36.02 ppm resonances.

h. The  $^{13}\text{C}$ -nmr spectrum of a sample of  $6\alpha$ -naltrexol which was partially deuterated in the 5 and 7 positions showed reduced intensities for the 90.51 and 22.97 ppm resonances.

i. The  $^{13}\text{C}$ -nmr spectrum of a sample of  $6\beta$ -naltrexol which was partially deuterated in the 5 and 7 positions showed reduced intensities for the 95.78 and 26.00 ppm resonances.

j. The  $^{13}\text{C}$ -nmr spectrum of a sample of naltrexone which was partially deuterated in the 15, 16-position showed reduced intensities for the 30.44 and 43.88 ppm resonance.

Table B-4. Carbon-13 NMR chemical shifts of 6,14-endo-Etheno-and 6,14-endo-Ethanotetrahydrothebaine system.<sup>a,b,19</sup>

Identification of Carbon <sup>c</sup>	6a <sup>e</sup>	6b <sup>e</sup>	6c <sup>e</sup>	6d <sup>e</sup>	5a <sup>e</sup>	5b <sup>e</sup>	5c <sup>e</sup>	5d <sup>e</sup>
1	119.15	119.44	119.05	119.00	119.05	119.34	118.95	119.59
2	113.39	116.27	113.69	113.63	113.83	116.66	114.03	114.76
3	141.59	137.58	141.58	141.53	141.63	137.58	141.49	142.22
4	147.76	146.60	147.92	147.87	146.60	145.60	146.80	147.05
5	95.00	98.81	98.61	98.61	94.47	97.05	96.76	96.22
6	81.02	83.98	83.98	83.93	77.40	80.42	80.18	79.64
7	50.47	46.43	48.48	46.52	49.40	47.69	47.65	47.45 <sup>b</sup>
8	29.74	30.42	30.86	30.43	30.23	32.14	32.23	31.45 <sup>b</sup>
9	59.76	59.83	59.83	59.79	61.21	58.33	61.16	59.40
10	22.21	22.13	22.09	22.04	21.84	22.77	21.75	28.87
11	127.96	127.19	128.22	128.22	128.56	127.54	128.61	125.73
12	133.78	133.73	134.12	134.12	132.31	132.17	132.32	130.22
13	47.24	47.20 <sup>b</sup>	47.01	46.94	45.60	47.06	46.04	45.60
14	43.01	42.67 <sup>b</sup>	42.71	42.62	35.41	35.94	35.89 <sup>h</sup>	35.30
15	33.26	33.31 <sup>g</sup>	33.40	33.40	35.02	35.35	35.36 <sup>h</sup>	33.30
16	45.24	45.40 <sup>g</sup>	45.35	45.30	45.06	43.70	45.01 <sup>h</sup>	41.35
17	125.73	124.60	124.71	125.00	17.36	17.50 <sup>b</sup>	17.41	17.02 <sup>b</sup>
18	135.66	135.14	135.05	134.99	28.46	29.55 <sup>b</sup>	29.75	31.55 <sup>b</sup>
19	208.68	75.25	73.25 <sup>b</sup>	74.67	210.54	74.57 <sup>b</sup>	74.18 <sup>b</sup>	73.89 <sup>b</sup>
20	30.23	23.89 <sup>b</sup>	25.16 <sup>b</sup>	23.89	33.60	24.77 <sup>b</sup>	24.72 <sup>b</sup>	24.72 <sup>b</sup>
21		42.87	28.57 <sup>b</sup>	43.06		29.79 <sup>b</sup>	29.75	29.55 <sup>b</sup>
22		15.65		15.70				
23		14.53		14.58				
3 OCH <sub>3</sub>	56.46		56.72	56.62	56.62		56.77	56.67
6 OCH <sub>3</sub>	53.24	55.06	55.06	54.92	52.09	52.52	52.57	52.67
NCH <sub>3</sub>	43.31	43.35	43.40	43.35	43.36		43.35	

Table B-4. (continued)

Identification of Carbon <sup>d</sup>	6a <sup>e</sup>	6b <sup>e</sup>	6c <sup>e</sup>	6d <sup>e</sup>	5a <sup>e</sup>	5b <sup>e</sup>	5c <sup>e</sup>	5d <sup>e</sup>
NCH <sub>2</sub>					59.79			
					9.11			
CH <sub>2</sub>					3.99			
CH <sub>2</sub>					3.31			
N-CN							117.88	

a,b,c,d,e,f. See Footnotes to Table B-2.

g. The <sup>13</sup>C-nmr spectrum of etorphine which was partially deuterated in the 15,16-positions showed reduced intensities for the 33.31 and 45.40 ppm resonances.

h. The <sup>13</sup>C-nmr spectrum of a sample of diprenorphine which was partially deuterated in the 15,16-positions showed reduced intensities for the 35.36 and 45.01 ppm resonances.

Table B-5.  $^{13}\text{C}$  Chemical shift data on some analgesics,  $\delta_c$  in  $\text{D}_2\text{O}^a$   $\delta_c$ .

Carbon No.	Compound																								
	2j	2k	2l	2m	2n	2o	9f	9i	9j	9k	10a	10b	10c	10d	10e	10f	10g	10h	10i	10j	10k	11a	11b	11c	11d
1' 123.3	122.0	123.8	123.6	123.5	122.7	131.2	131.6	131.6	131.9	130.1	130.1	131.9	131.6	129.9	131.8	131.2	132.0	132.6	131.5	130.5	132.9	132.6	132.2	132.6	133.0
2 121.0	120.7	121.6	121.5	121.3	120.8	113.8	114.5	114.4	114.4	113.7	120.0	115.0	114.8	113.4	115.3	115.0	115.2	116.0	117.2	117.4	116.4	116.6	116.7	116.1	116.2
3 141.0	139.5	141.5	142.1	141.4	142.0	156.8	157.5	157.3	157.4	156.2	150.4	157.8	157.2	155.6	157.7	157.1	166.5	167.4	156.5	157.0	158.8	158.9	158.2	158.5	159.2
4 145.0	147.5	145.9	146.7	145.3	145.4 <sup>b</sup>	116.2	117.0	116.4	116.7	115.6	121.2	117.0	116.9	115.3	117.2	116.4	117.4	118.0	117.4	117.8	116.8 <sup>b</sup>	116.9	117.6	116.5	117.4
5 91.5	90.9	92.4	91.9	91.8	90.9	35.2 <sup>b</sup>	36.0 <sup>b</sup>	41.3	41.4	25.2	24.8	26.4	25.9	25.6	26.3	26.8	30.3	26.4	148.2	147.3	45.5	52.1	38.3	44.9	217.5
6 214.0	57.8	214.0	214.2	214.3	146.7 <sup>b</sup>	21.9 <sup>b</sup>	22.6 <sup>b</sup>	23.6 <sup>b</sup>	23.9 <sup>b</sup>	--	--	--	--	--	--	--	8.9	--	130.8	131.7	20.5	26.0	20.2	20.3	33.1
7 36.5	24.2	37.5	37.0	37.1	28.9 <sup>c</sup>	22.6 <sup>b</sup>	23.2 <sup>b</sup>	25.1 <sup>b</sup>	25.5 <sup>b</sup>	--	--	--	--	--	--	--	129.2	129.5	16.3	25.6	20.2	16.0	10.3		
8 29.5	28.3	30.2	29.8	29.6	29.6 <sup>c</sup>	30.4	28.3	27.1	27.9 <sup>c</sup>	14.3	13.8	15.0	14.9	14.8	15.1	15.0	14.4	14.8	129.6	15.1	--	25.6	--	--	
9 65.4	64.3	65.3	64.9	64.9	65.4	63.1	64.0	60.4	61.1 <sup>c</sup>	59.7	59.0	61.8	61.3	60.3	61.7	55.0	61.9	68.4	57.6	61.5	65.8	66.7	64.0	67.4	43.8
10 25.5	25.7	25.8	25.7	25.5	26.1	27.0	27.1	28.1 <sup>c</sup>	23.7	24.8	25.5	25.7	24.2	25.3	29.6	190.5	191.7	28.6	30.1	--	--	--	--	--	--
11 124.1 <sup>1</sup>	124.8	124.6	124.4	124.4	124.5	126.6	127.2	127.9	127.9	125.7	131.9	127.2	127.1	125.3	127.4	127.5	127.4	127.6	128.0	128.0	121.4	121.5	122.6	121.2	121.0
12 129.7	131.2	130.2	130.1	129.9	131.7	142.3	142.8	141.8	141.5	142.3	142.0	143.5	143.1	141.6	143.8	143.4	152.0	144.8	147.0	148.1	147.6	144.0	147.4	143.0	
13 51.5	47.4	52.0	51.8	51.6	49.4	41.7	42.2	38.4	38.5	36.6	36.3	37.5	37.3	36.6 <sup>c</sup>	37.8	37.6	40.7	38.5	42.2	46.0	52.8	52.8	56.7	53.1	55.5
14 72.9	72.5	73.5	73.2	73.1	74.1	72.2	72.8	44.8	44.8	40.2	39.2	40.5	40.0	40.6	42.0	40.2	38.7	44.2	32.0	40.3	--	--	--	31.2	
15 32.9	31.0	33.5	33.2	33.3	33.9	32.8	33.5	37.0	37.2	40.1	39.2	40.5	40.0	40.6	41.8	40.1	34.9	39.5	40.0	31.1	36.7	37.5	35.3	36.8	31.2
16 48.0	49.1	49.0	48.7	49.1	49.4	48.6	50.0	48.5	47.7	47.9	46.8	48.1	48.5	48.1	48.7	40.3	49.6	50.0	49.1	50.7	55.7	55.7	55.0	57.2	43.8
17 53.9	60.1	58.7	60.7	60.5	58.3	59.6	60.9	58.5	57.2	49.7	48.9	51.4	51.6	60.3	54.9	--	62.8	63.2	45.8	57.7	63.7	63.8	60.7	44.5	
18 113.9	32.5 <sup>b</sup>	128.6	7.0	32.8 <sup>b</sup>	128.5 <sup>b</sup>	7.3	33.1	128.5	32.2	115.1	114.8	111.3	145.9	7.8	114.5	--	8.0	7.9	74.6	57.7	9.1	9.1	128.0	--	
19 147.5	27.4 <sup>b</sup>	129.2	5.2 <sup>b</sup>	27.8 <sup>b</sup>	128.9	4.4 <sup>c</sup>	27.1 <sup>c</sup>	128.8	140.1	146.1	145.7	156.5	147.9	6.1	148.0	--	6.3 <sup>b</sup>	6.2 <sup>b</sup>	82.8	147.3	5.6	6.0	129.2	--	
20 27.4	20.2 <sup>b</sup>	--	7.4 <sup>b</sup>	20.6	--	6.6 <sup>c</sup>	20.5	--	133.0	146.1	145.7	145.0	113.7	6.1	28.0	--	7.0 <sup>b</sup>	6.6 <sup>b</sup>	--	130.5	5.6	6.0	--	--	
21 20.0	29.1 <sup>b</sup>	--	--	29.1 <sup>b</sup>	--	31.1 <sup>c</sup>	--	126.1	112.4	112.2	114.1	116.9	--	20.5	--	--	--	--	--	--	--	--	--	--	
	9f	9i	9j	9k	10b	10c	10a	10d	10i	10h	11a	11b													
	TARTRATE.										MONOSUCCINATE														
C <sub>1</sub>	C <sub>2</sub>	C <sub>1</sub>	C <sub>2</sub>	C <sub>1</sub>	C <sub>2</sub>	C <sub>22</sub>	C <sub>23</sub>	19-Me		METHANE SULFONATE	C <sub>1</sub>	C <sub>2</sub>	C <sub>1</sub>	C <sub>2</sub>											
75.7	180.2	75.4	178.4	75.2	178.5	131.3	173.7	21.8	13.1	41.2	40.2	41.0	41.0	41.1	34.0	182.0	34.0	180.2							

a. Samples were dissolved in  $\text{D}_2\text{O}$  containing 1,4-dioxane as an internal reference ( $\delta_c$  67.9).

b,c. These assignments may be interchanged in each column.

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