SYNTHESIS AND DETERMINATION OF THE ABSOLUTE CONFIGURATION OF 3-METHYL-6,7-BENZO-3- AZABICYCLO(331)NONEN-9-ONE; DEVELOPMENT OF A SECTOR RULE FOR THE OPTICALLY ACTIVE PHENYL CHROMOPHORE

E. JAMES CONNOR

Follow this and additional works at: https://scholars.unh.edu/dissertation

Recommended Citation

https://scholars.unh.edu/dissertation/917

This Dissertation is brought to you for free and open access by the Student Scholarship at University of New Hampshire Scholars' Repository. It has been accepted for inclusion in Doctoral Dissertations by an authorized administrator of University of New Hampshire Scholars' Repository. For more information, please contact Nicole.Hentz@unh.edu.
SYNTHESIS AND DETERMINATION OF THE ABSOLUTE CONFIGURATION OF 3-METHYL-6,7-BENZO-3-AZABICYCLO(331)NONEN-9-ONE; DEVELOPMENT OF A SECTOR RULE FOR THE OPTICALLY ACTIVE PHENYL CHROMOPHORE

Keywords
Chemistry, Organic
CONNOR, E. James, 1942-
SYNTHESIS AND DETERMINATION OF THE ABSOLUTE CONFIGURATION OF 3-METHYL-6,7-BENZO-3-
AZABICYCLO[3.3.1]NONEN-9-ONE; DEVELOPMENT OF A SECTOR RULE FOR THE OPTICALLY ACTIVE PHENYL CHROMOPHORE.

University of New Hampshire, Ph.D., 1970
Chemistry, organic

University Microfilms, Inc., Ann Arbor, Michigan

THIS DISSERTATION HAS BEEN MICROFILMED EXACTLY AS RECEIVED
SYNTHESIS AND DETERMINATION OF THE ABSOLUTE CONFIGURATION OF
3-METHYL-6,7-BENZO-3- AZABICYCLO[3.3.1]NONEN-9-ONE;
DEVELOPMENT OF A SECTOR RULE
FOR THE OPTICALLY ACTIVE PHENYL CHROMOPHORE

by

F. JAMES CONNOR

B.A., Kalamazoo College, 1964

A THESIS
Submitted to the University of New Hampshire
In Partial Fulfillment of
The Requirements for the Degree of
Doctor of Philosophy

Graduate School
Department of Chemistry
September, 1969
This thesis has been examined and approved.

Gloria H. Lee

James D. Morrison

Herbert S. Appleman

Charles V. Berne

J. John Uchtdorf

November 25, 1969
ACKNOWLEDGEMENT

The author wishes to express his appreciation to the many people who have contributed to the development of this thesis. In particular, he wishes to express his gratitude to Dr. Gloria G. Lyle for the direction and guidance which she has so generously given during the few short years of study with her.

The optically active 6,7-benzomorphans were supplied by Dr. Everett L. May of the National Institutes of Health, Bethesda, Maryland. Only because of his generosity could a large portion of this thesis be written.

The receipt of financial support for a large part of this work from the National Science Foundation, grants GP 3553 and 7344, is gratefully acknowledged.

The author wishes to express his gratitude to his wife, Helen, for her patience and tireless assistance in the construction of this thesis. It is dedicated to her.

James Connor
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIST OF TABLES</td>
<td>vi</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>vii</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>ix</td>
</tr>
<tr>
<td>I. INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>A. The Opium Alkaloids and Synthetic Analgesics.</td>
<td>1</td>
</tr>
<tr>
<td>B. Statement of Purpose</td>
<td>7</td>
</tr>
<tr>
<td>II. DISCUSSION AND RESULTS</td>
<td>9</td>
</tr>
<tr>
<td>A. The 6,7-Benzo-3-azabicyclo[3,3,1]nonene System</td>
<td>9</td>
</tr>
<tr>
<td>B. 1-Methyl-3-benzal-4-piperidone (15b)</td>
<td>20</td>
</tr>
<tr>
<td>C. Reduction Products of 15a</td>
<td>26</td>
</tr>
<tr>
<td>D. 1-Methyl-3-benzal-4-piperidinol (28)</td>
<td>29</td>
</tr>
<tr>
<td>E. Attempted Cyclization of Alcohol 16 to Form 17</td>
<td>30</td>
</tr>
<tr>
<td>F. The Mannich Condensation</td>
<td>32</td>
</tr>
<tr>
<td>G. Attempted Preparation of 2'-Methoxy-3-methyl-6,7-benzo-3-azabicyclo[3,3,1]nonen-9-one (34)</td>
<td>36</td>
</tr>
<tr>
<td>H. Resolution of 3-Methyl-6,7-benzo-3-azabicyclo[3,3,1]nonen-9-one (31)</td>
<td>40</td>
</tr>
<tr>
<td>I. Electronic Spectra of 3-Methyl-6,7-benzo-3-azabicyclo[3,3,1]nonen-9-one (31)</td>
<td>41</td>
</tr>
<tr>
<td>J. Optical Rotatory Dispersion and Circular Dichroism Spectra of 31</td>
<td>44</td>
</tr>
<tr>
<td>K. Application of the Octant Rule to 31 for Determination of the Absolute Configuration</td>
<td>51</td>
</tr>
<tr>
<td>L. The 6,7-Benzomorphans (7)</td>
<td>53</td>
</tr>
<tr>
<td>M. Ultraviolet Spectra of 7</td>
<td>53</td>
</tr>
</tbody>
</table>
## LIST OF TABLES

<table>
<thead>
<tr>
<th>Number</th>
<th>Table Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>$R_{2u} \leftrightarrow A_{1g}$ Cotton Effect of the 6,7-Benzomorphans (Z)</td>
<td>60</td>
</tr>
<tr>
<td>2.</td>
<td>$R_{1u} \leftrightarrow A_{1g}$ Cotton Effect of the 6,7-Benzomorphans (Z)</td>
<td>63</td>
</tr>
</tbody>
</table>
**LIST OF FIGURES**

<table>
<thead>
<tr>
<th>Number</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Infrared Spectrum of 1-Methyl-3-benzal-4-piperidone (15a)</td>
<td>13</td>
</tr>
<tr>
<td>2.</td>
<td>NMR Spectrum of 1-Methyl-3-benzal-4-piperidone (15a)</td>
<td>14</td>
</tr>
<tr>
<td>3.</td>
<td>Infrared Spectra of 15a in the Region of Hydroxyl and Carbonyl Absorptions</td>
<td>16</td>
</tr>
<tr>
<td>4.</td>
<td>Infrared Spectrum of Enol Acetate 19</td>
<td>18</td>
</tr>
<tr>
<td>5.</td>
<td>NMR Spectrum of Enol Acetate 19</td>
<td>19</td>
</tr>
<tr>
<td>6.</td>
<td>Ultraviolet Spectra of 15c and 15b</td>
<td>22</td>
</tr>
<tr>
<td>7.</td>
<td>Geometrical Relationships Between Biphenyl, 15a and 15b</td>
<td>25</td>
</tr>
<tr>
<td>8.</td>
<td>Infrared Spectrum of Reduction Product 16</td>
<td>28</td>
</tr>
<tr>
<td>9.</td>
<td>Infrared Spectrum of 31</td>
<td>37</td>
</tr>
<tr>
<td>10.</td>
<td>NMR Spectrum of 31</td>
<td>38</td>
</tr>
<tr>
<td>11.</td>
<td>UV Spectra of 31 in Various Solvents</td>
<td>42</td>
</tr>
<tr>
<td>12.</td>
<td>ORD and CD Spectra of 31 in EPA</td>
<td>45</td>
</tr>
<tr>
<td>13.</td>
<td>CD Spectrum of 31 in Basic Methanol</td>
<td>48</td>
</tr>
<tr>
<td>14.</td>
<td>ORD Spectrum of 31 in Basic Methanol</td>
<td>49</td>
</tr>
<tr>
<td>15.</td>
<td>Sector Rule for ( \beta,\gamma )-Unsaturated Ketones</td>
<td>51</td>
</tr>
<tr>
<td>16.</td>
<td>( \beta,\gamma )-Unsaturated Ketone Rule Applied to 31</td>
<td>52</td>
</tr>
<tr>
<td>17.</td>
<td>UV Spectra of 7a in Methanol as Free Base and Hydrochloride</td>
<td>54</td>
</tr>
<tr>
<td>18.</td>
<td>ORD, CD and UV Spectra of 7c-HBr in Methanol</td>
<td>56</td>
</tr>
<tr>
<td>19.</td>
<td>ORD Spectra of 7a as Free Base and Hydrochloride</td>
<td>58</td>
</tr>
<tr>
<td>20.</td>
<td>CD Spectra of (+)-7d as Free Base and Hydrochloride</td>
<td>59</td>
</tr>
<tr>
<td>21.</td>
<td>CD Spectra of 7e as Free Base and Hydrochloride</td>
<td>62</td>
</tr>
<tr>
<td>Number</td>
<td>Description</td>
<td>Page</td>
</tr>
<tr>
<td>--------</td>
<td>-----------------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>22.</td>
<td>CD Spectra of $7^f$ as Free Base and Hydrobromide.</td>
<td>64</td>
</tr>
<tr>
<td>23.</td>
<td>ORD Spectra of $7^f$ as Free Base and Hydrobromide.</td>
<td>65</td>
</tr>
<tr>
<td>24.</td>
<td>ORD and CD Spectra of $7b-HSr$ in $H_2O$</td>
<td>67</td>
</tr>
<tr>
<td>25.</td>
<td>Nodal Planes in the $\pi_4$ and $\pi_5$ Orbitals of Benzene</td>
<td>70</td>
</tr>
<tr>
<td>26.</td>
<td>(-)-Benzomorphan as Viewed Along $2',7$-Axis</td>
<td>71</td>
</tr>
<tr>
<td>27.</td>
<td>(-)-Benzomorphan as Viewed Along $3',6$-Axis</td>
<td>72</td>
</tr>
<tr>
<td>28.</td>
<td>(-)-Benzomorphan as Viewed Along Midway Axis</td>
<td>73</td>
</tr>
<tr>
<td>29.</td>
<td>Projection of $41$</td>
<td>75</td>
</tr>
<tr>
<td>30.</td>
<td>Projection of $42$</td>
<td>76</td>
</tr>
<tr>
<td>31.</td>
<td>Projection of $43$ and $44$ Along the Midway Axis</td>
<td>78</td>
</tr>
<tr>
<td>32.</td>
<td>Projection of $45$</td>
<td>79</td>
</tr>
<tr>
<td>33.</td>
<td>Projection of Dihydrocodeine ($46$)</td>
<td>80</td>
</tr>
<tr>
<td>34.</td>
<td>Projection of Codeine ($2$)</td>
<td>81</td>
</tr>
<tr>
<td>35.</td>
<td>Thebaine Projection</td>
<td>83</td>
</tr>
<tr>
<td>36.</td>
<td>Lycorine Projection</td>
<td>84</td>
</tr>
<tr>
<td>37.</td>
<td>Projection of (-)-$31$</td>
<td>86</td>
</tr>
</tbody>
</table>
ABSTRACT

SYNTHESIS AND DETERMINATION OF THE ABSOLUTE CONFIGURATION OF
3-METHYL-6,7-BENZO-3-AZAPICYCLO[3,3,1]NONEN-9-ONE;
DEVELOPMENT OF A SECTOR RULE
FOR THE OPTICALLY ACTIVE PHENYL CHROMOPHORE

by

JAMES CONNOR

The 6,7-benzomorphan (I) analog, 3-methyl-6,7-benzo-
3-azabicyclo[3,3,1]nonen-9-one (II) (nitrogen at position 3
instead of 2), was prepared via the Mannich reaction with β-
tetralone, CH₃NH₂ and HCHO. Resolution was accomplished with
(+)-tartaric acid. The uv, ord, and cd spectra were determined
in various solvents and are discussed. The uv spectra give
evidence of homoconjugation of the β,γ-unsaturated ketone
(ε₂₉₀ 1170), but ord and cd spectra give only little support
to this (θ⁻¹⁷₀ 304 572°).

\[ \text{I} \quad \text{II} \quad \text{III} \]
An alternate synthetic route to III was attempted, the first step being an aldol condensation of 1-methyl-4-piperidone and benzaldehyde; this gave both geometrical isomers of 1-methyl-3-benzaI-4-piperidone (IV). Both isomers exist preferentially as the enol tautomers. Attempted reduction of IV to 1-methyl-3-benzyl-4-piperidinol (V) by several methods gave products which appeared to trap or occlude hydrocarbon solvents from which they could be separated only by strong heating. Attempted cyclization of V to III with PPA and with $\text{P}_4\text{O}_{10}$ gave only unsaturated products.

The ORD, CD, and UV spectra of a series of derivatives of I were recorded for the free bases and hydrohalide salts. In a normal CD spectrum the compounds exhibit a long wavelength Cotton effect near 280 nm, and a second, antipodal Cotton effect near 230 nm. The only exceptions are the base forms of N-phenethyl derivatives, in which cases the 230 nm band exhibits reversal of sign. The ORD and CD spectra of $\text{E}(-)3,5,9$-trimethyl-I were recorded from 325-185 nm. In both modes an intense Cotton effect was observed at 188 nm ($[\Theta]_{max} = -54000^\circ$).

A sector rule for the phenyl chromophore was postulated for the Cotton effect at 280 nm. Application of this to ORD and CD spectra of a number of morphinan and morphine derivatives gives excellent correlation in every case.

The D-line and $\text{Hg}_546$-line rotations are reported for derivatives of I.
INTRODUCTION

The Opium Alkaloids and Synthetic Analgesics

Few natural products have been utilized as beneficially and deleteriously for the well-being of mankind as the opium alkaloids. The powers of producing analgesia, euphoria, hallucinosis, and addiction have brought to them attention which, at times, has rivaled that given the more elementary chemical, ethanol.

The first chemical manipulations performed on the crude natural product are probably lost forever in history, but one might take the liberty to surmise that they were not directed toward the enhancement of the medicinal aspects of the substance. However, by the beginning of the last century, more altruistic goals were being pursued and in 1806 M. Chaptal wrote:

"Opium contains a strong and narcotic (sic) aroma, from which it is impossible to clear it...

"By long digestion in hot water the volatile oil becomes attenuated, is disengaged, and carries the aroma with it; so that by this means the oil and aroma may be separated, at least for the most part. It has been observed that opium deprived of this oil, a portion of its aroma, and its resin, preserved its sedative virtue, without being narcotic (sic) and stupifying."

A quarter of a century later it is apparent that a great deal had been learned of the nature of opium, and chemists were beginning to recognize it as a complicated mixture:

"Morphia is the narcotic (sic) principle of
opium. Opium, besides morphia, contains meconic acid, narcotine, gum, resinous, extractive and colouring matter, and a small quantity of caoutchouc, or Indian rubber.

"Morphia exists in the opium, combined with meconic acid, forming meconate of morphia..."2

After a description of the extraction procedure of both "morphia" and narcotine, it is stated of the latter:

"The unpleasant properties of opium as a medicine, are attributed to this substance, and perhaps the different effects of the salts of morphia from opium, are only owing to their not containing narcotine."2

Of course it is now known that opium is much more complex than even this. A rather large number of alkaloids have been isolated from the substance, among the more important being morphine (1), codeine (2), and thebaine (3).

![Chemical structures]

1 2 3

It is well known that the pure substances are still not without deleterious effects. Chemists have endeavored to modify the structure in a manner such that analgesia may be produced while undesirable properties may be diminished or eliminated.

Systematic changes of the morphine molecule to modify
the analgesic properties were, for the most part, paralleled by changes in addiction liability. Various attempts were made, with little success, to synthesize molecules containing the analgesic-producing portion of morphine but hopefully lacking the other properties. The basic molecule was considered as a phenanthrene, a dibenzofuran, a piperidine, and others. In 1939 Eisleb and Schauman prepared meperidine (4) which was found to exhibit morphine-like activity.

\[ \text{Chemical Structures} \]

The development of methadone (5) led researchers to investigate the possibility of analgesia-producing activity in morphinans (6) and 6,7-benzomorphans (7).
May and co-workers\textsuperscript{4} have described the preparation and medicinal properties of a large number of derivatives of 7, some of which have become quite important as analgesic agents.

The ring system of 7 possesses two asymmetric carbon atoms, \( C_1 \) and \( C_5 \). The number of stereoisomers is restricted by ring strain at the bridgehead positions in such a manner that when \( R_2 \) is hydrogen there exists only one enantiomeric pair. When \( R_2 \) is not hydrogen, the substituent may be either cis or trans with respect to \( R_1 \). Thus, for each enantiomer, there exists the possibility of two diastereomers which are designated for cis and trans as "a" and "\( \beta \)" respectively. For every compound in the series there should exist two enantiomeric pairs which can be separated by standard techniques; the enantiomeric pairs may be resolved into the optically active antipodes. This has been accomplished by E. L. May and co-workers\textsuperscript{4}, leading to the observation that the \textit{levor}-isomer possesses most of the analgesic activity in this series.\textsuperscript{4,9}
The resolution of these compounds is of even broader interest to the organic chemist. Most natural products occur in optically active forms if molecular dissymmetry exists. In many instances, synthetic compounds of opposite configuration possess little or none of the activity of the natural product. Hence it is of considerable importance to know the absolute configuration of both the natural products under consideration and the synthetic derivatives prepared to emulate them. It would be inefficient to prepare and resolve a racemic modification if it were possible to synthesize directly the desired stereoisomer. This, however, presupposes either a foreknowledge of the absolute configuration or a straightforward method of determining it. Both of the methods considered to give unequivocal results, degradation to compounds of known configuration and X-ray analysis, are laborious and time-consuming.

Except in reactions with other dissymmetric species, enantiomers behave identically chemically, and, for the most part, exhibit identical spectroscopic properties. The exception is their interaction with plane-polarized and circularly-dichroised light to give optical rotatory dispersion and circular dichroism spectra.

The well-known octant rule\textsuperscript{10,11} for ketones has been employed to ascertain the absolute configurations of large numbers of compounds. Of course many organic compounds do not contain the carbonyl function which is necessary for utilization of this method. However, the success of the octant
rule has led researchers to seek similar "rules" for other chromophores. Once it had been ascertained that the phenyl group situated in a dissymmetric environment was capable of exhibiting optical activity, attempts were made to formulate such a rule for it.

Among the first systems used for models were the Amaryllis alkaloids including crinine (8) and lycorine (9) and related compounds, and the morphine alkaloids. In many respects these compounds were well chosen for study; they represent a wide range of stereochemistry, and the aromatic ring is rigid with respect to the remainder of the molecule (a necessary prerequisite). However, these compounds often contain other functional groups which themselves are capable of demonstrating optical activity, thereby complicating the spectra of the chromophore under study.

The benzomorphans not only exhibit the above advantages but are nearly devoid of complicating functional groups,
and the compounds were made available for study in optically active form. The ord and cd spectra had not been reported when this investigation was begun, and a systematic study of these compounds might provide sufficient information to formulate a sector rule for the 6,7-benzomorphans, the morphinans, and related compounds.

In support of this work it seemed desirable to synthesize a new series of benzomorphan-like compounds. This would introduce a new series of compounds for biological testing and provide a comparison to the spectral data obtained for the benzomorphans. The requirement for this unique system was that the compound retain the benzomorphan ring system without the introduction of additional chromophores. The logical choice involved changing the position of the nitrogen in the ring system.

Since placing the heteroatom in either the 5 or 8 position would give an aniline chromophore and not the phenyl or phenoxy system present in the model, and since placing it in the bridgehead (1) position would give an isoquinoline and hence a crinine (8)- or lycorine (9)-like system, it was deemed advisable to place it at either position 3 or 4.

Purpose of This Investigation

The objective of this dissertation was to prepare compounds isomeric with the 6,7-benzomorphans (7), differing chiefly in the position of the nitrogen atom. These would be resolved and the ord and cd spectra determined. The results of these spectra would be compared to those obtained
from a series of benzomorphans with the expectation of pos-
tulating a sector rule. The new compounds prepared would
be submitted to appropriate agencies or pharmaceutical houses
for screening for biological activities.
DISCUSSION AND RESULTS

The 6,7-Benzo-3-azabicyclo[3,3,1]nonene System

A substance which appeared to satisfy the criteria set forth for a unique benzomorphan analog is 6,7-benzo-3-azabicyclo[3,3,1]nonene (10). The ring system had not previously been reported, it meets the criterion of inherent dissymmetry within a fused ring system, and, differing only in the position of the nitrogen heteroatom, it bears a close similarity to the 6,7-benzomorphans (7).

A plausible synthetic route might be based on the following dehydration-cyclization reaction reported by Cook and Hewett.\(^\text{14}\) The alcohols 11, 12, and 13 gave 6,7-benzo-bicyclo[3,3,1]nonene (14) in yields of 70, 55, and 30 percent respectively.
Using this as a model system, it seemed apparent that if the cyclohexane ring were substituted by a piperidine ring, and if the cyclization would proceed as smoothly as in the carbocyclic system, this would be an excellent method of preparing a series of compounds belonging to the ring system 10.

In 1946 McElvain and Rorig\(^\text{15}\) reported that simple base catalyzed condensation of 1-methyl-4-piperidone and benzaldehyde gave 1-methyl-3-benzal-4-piperidone \((15)\), a promising starting material.
Reduction of $15$ to the corresponding alcohol ($16$), followed by cyclization, would give 3-methyl-6,7-benzo-3-azabicyclo[3.3.1]nonene ($17$).

The aldol condensation generally gave good yields of $15$ with the major modifications consisting of greatly increasing the concentration of the reactants and periodically removing the light yellow solid which slowly formed. The major product $15a$ was identical to that reported; an isomeric yellow solid ($15b$) was isolated and is discussed below.
The major product, 15a, is nearly white and melts at a relatively high temperature (226°). Examination of the infrared spectrum (Fig. 1) revealed that the only band which might be ascribed to the carbonyl function was one of medium intensity at 1640 cm⁻¹, well outside the normal range of α,β-unsaturated ketones. For comparison, the spectrum of dibenzalacetone (18) was determined. It also showed no carbonyl absorption within the normal range of 1665-1685 cm⁻¹.

\[
\text{18}
\]

After reduction of 15a by several methods gave an apparent mixture of compounds (other than the two possible diastereomers) and generally inconsistent results, verification of the structural assignment of 15 to the product obtained in the aldol condensation was sought. The infrared spectrum, while showing bands at 695 and 725 cm⁻¹, consistent for monosubstituted benzene, failed to exhibit the expected carbonyl band. The high melting point cast more doubt. The nmr spectrum, Fig. 2, was not readily interpreted. The singlet at 7.25 ppm was assigned to the phenyl protons, and the singlet at 2.1 ppm to the N-CH₃ protons. The small singlet at 7.05 ppm
Fig. 1. Infrared Spectrum (mull) of 1-Methyl-3-benzal-4-piperidone (Isomer a)
Fig. 2. NMR Spectrum (CDCl₃) of 1-Methyl-3-benzal-4-piperidone (Isomer a)
was assigned to the vinyl proton. If the integration of the phenyl and vinyl group were considered to represent six protons, the remainder of the spectrum represented eleven, the expected number.

Elemental analyses of 15a and the picrate and oxime derivatives gave values within 0.3% of the calculated values, indicating that an empirical formula of C₁₃H₁₅NO was correct. The possibility of dimeric or larger species was discounted beyond reasonable doubt by the molecular weight determination.

The anomaly of the weak carbonyl absorption was resolved by further investigation of the infrared absorption. When the spectrum was determined as a halocarbon mull, there appeared a broad absorption at 3100 cm⁻¹, which persisted even after recrystallization and prolonged drying. A determination of the spectrum in CHCl₃ showed a sharp band of medium intensity at 3580 cm⁻¹ and a broad peak at about 3200 cm⁻¹ while the band at 1640 cm⁻¹ was weakened in intensity (Fig. 3). These data are consistent with the possibility of a mixture of keto-enol tautomers, which was verified by a positive ferric chloride test for enols.¹⁷

Although the nmr spectrum did not exhibit an enol proton between 8 and 16 ppm,¹⁸ this was not considered proof of its absence. The substance is not sufficiently soluble in common solvents to give a favorable signal to noise ratio for very broad bands of low intensity. It was noted that shaking the solution in deuterochloroform with D₂O caused a peak at 4.05 ppm to become reduced in intensity, probably
Fig. 3. Infrared Spectra of 15a in the Region of Hydroxyl and Carbonyl Absorptions: Top, mull; Bottom, CHCl₃ Solution
the result of proton exchange at the 5-position.

\[
15a + (\text{CH}_3\text{CO})_2\text{O} \rightarrow \text{C}_{6}\text{H}_5\text{N}
\]

Preparation of the enol acetate (19) gave a product which exhibited infrared (Fig. 4) and nmr spectra (Fig. 5) very similar to those of the parent compound 15a. The acetate band (1750 cm\(^{-1}\)) and the nmr signals at 1.96 and 2.01 ppm (N-CH\(_3\) and OCOCH\(_3\)) were consistent with the assignment. Two vinyl protons were anticipated but only one appeared at 6.7 ppm (singlet). The other, which should have appeared as a triplet, did not resonate in the expected region of 5.2-7.7 ppm. Two signals near 3.6 ppm (J=12.5 Hz) appeared to represent part of a triplet with the third branch appearing as a shoulder under a large peak at 3.43 ppm. A comparison with other known enol acetates showed the range of values for such protons to be more extensive than expected. Vinyl acetate (20), for example, is reported to give signals at 4.55 (a), 4.85 (b), and 7.25 (c) ppm. Both of the vinyl protons of compound 21 are reported to resonate at 3.85 ppm.
Fig. 4. Infrared Spectrum (mull) of Enol Acetate
Fig. 5. NMR Spectrum (CDCl₃) of Enol Acetate 19
Hydrolysis of the acetate ester 19 gave nearly quantitative recovery of the parent compound 15a and demonstrated unequivocally that O-acylation had occurred.

1-Methyl-3-benzal-4-piperidone (15b)

Isomeric 15b was isolated from the aldol reaction in yields as high as 17 percent. Initially, it was assumed to be the keto-alcohol 22 which McElvain and Rorig\textsuperscript{15} had reported isolating from this reaction. Compound 22 exhibited a melting point (115-126\textdegree) similar to that of crude 15b, which, after purification, melted at 124.0-126.5\textdegree. The melting points of the hydrochlorides were also similar; 22 melted at 230-235\textdegree while 15b, which formed a stable hydrated salt with one third mole of water, decomposed at 234-236\textdegree. Drying in vacuo easily drove off the water giving the anhydrous salt melting at 225-227\textdegree.
The bright yellow color of 15b did not seem consistent for the isolated non-conjugated chromophores of 22. The spectra of 15b, in general, bore a strong resemblance to those of 15a. The infrared spectrum, determined as a mull, showed a very broad, diffuse band between 3100 and 3400 cm\(^{-1}\), but seemingly not strong enough to result from an alcohol function. A band of medium intensity at 1720 cm\(^{-1}\) was quite suggestive of a carbonyl group, but again it was of low intensity. Bands at 755 and 695 cm\(^{-1}\) were consistent, however, with a monosubstituted phenyl.

The ultraviolet spectrum, when compared to that of 15a (Fig. 6) gave the initial clue to its identity; the two spectra were quite similar, the intense band at 287 nm being inconsistent with the keto-alcohol 22.
Fig. 6. Ultraviolet Spectra (ethanol) of 15a and 15b

The uv spectrum of 15a exhibits a strong band at 290 nm, assigned to the $\Phi$-C=C-C=O chromophore, in good agreement with the model compounds 23 and 24.

![Molecular structures](image)

Compound 23 exhibits a band at 286 nm ($\varepsilon$ 22500)$^{22}$ and 24 exhibits a band at 290 nm ($\varepsilon$ 18000)$^{23}$. The similarity
of the spectra of 15a and 15b suggested a cis/trans relationship, and the elemental analysis of the hydrochloride was consistent with this hypothesis. The infrared spectrum of 15b (CHCl₃) shows a sharp alcohol peak of weak intensity at 3595 cm⁻¹ and a broad, hydrogen-bonded hydroxyl band at 3400 cm⁻¹, behavior similar to 15a. This indicated that it also underwent keto-enol tautomerism.

It was observed that the isomer obtained as the minor product, 15b, was easily converted to its isomeric form 15a. Heating 15b in refluxing ether gave 15a. Attempted purification of the lower melting 15b frequently gave small amounts of the higher melting form; attempted esterification at elevated temperatures gave predominantly the enol acetate ester of isomer a. From the infrared and nmr spectra, both obtained in solution, it was known that the two forms were not simply different crystalline forms of one compound; thin layer chromatography data supported this. The two isomers gave greatly different R_f values and a mixture of the two isomers gave two distinct spots with R_f values identical to those of the pure forms.

The higher melting isomer a was converted to b by irradiation with ultraviolet light, suggesting that 15a was the more stable and, probably, trans-isomer. The cis-isomer would be badly crowded due to interaction between the phenyl group and the ketone, but the enol form might exhibit strong intramolecular hydrogen bonding to the ring. Furthermore, to avoid severe crowding, the phenyl must twist from coplanarity, thus diminishing conjugation; it would be expected
that the molar absorptivity would be substantially lowered. In Fig. 6 it is shown that isomer b has a lower extinction coefficient than a.

The phenyl group of the trans-isomer cannot come within close proximity of the carbonyl-enol group; hence, intramolecular hydrogen bonding cannot occur. The only unfavorable interaction is with the hydrogen atoms on position 2. Models indicate that this can be relieved substantially by a deviation from co-planarity by about 30-40°, an angle not large enough to forbid overlap of the π orbitals of the unsaturated system.

\[
\begin{align*}
\text{15a} \\
\end{align*}
\]

Inspection of the infrared spectra obtained at various concentrations in chloroform did, in fact, show that the relative intensities of the free hydroxyl and bonded hydroxyl
peaks remained nearly constant in the case of isomer b, but that the relative intensities were not constant for various concentrations of isomer a.

The crowding in the cis-isomer, b, probably accounts for the apparent lack of success in obtaining a cis-enol acetate. When the reaction conditions were severe enough, isomerization occurred, giving the trans-isomer (19).

It is of interest to note that both isomers, lacking planes of symmetry, since they cannot exist in planar configurations, are inherently dissymmetric species. This can be best illustrated, as in Fig. 7, by comparing the systems to a biphenyl (25) which is known to be capable of both dissymmetry and optical activity.

Fig. 7. Geometrical Relationships Between Biphenyl, 15a and 15b

The biphenyls can be resolved only when substituents are present on the ortho-positions, a condition which, due
to steric interactions, sufficiently increases the energy barrier to rotation about the biphenyl axis. This is also the case with the trans-isomer, 15a, but models indicate that it might be possible to resolve the cis-isomer, 15b. Resolution of both isomers should be possible if the phenyl group bore an ortho-substituent.

Reduction Products of 15a

Attempts were made by several methods to reduce 15a to the saturated alcohol 16:

\[ 15a \xrightarrow{H_2/PtO_2} 16 \]

\[ 15a \xrightarrow{PtO_2} 16 + \quad \xrightarrow{LiAlH_4} 16 \]

\[ 15a \xrightarrow{H_2/PtO_2} 19 \xrightarrow{LiAlH_4} 16 \]
Reduction over platinum oxide (equation A) gave a mixture of what appeared to be the alcohol 16 and the partially reduced ketone 26. Attempts to obtain complete reduction over platinum led, in every case, to a mixture which, based on infrared and ultraviolet spectral data, contained both 16 and 26. Since it has been reported that 4-piperidones readily form hydrates, perhaps as 24 was formed in the hydrogenation flask, it was converted to a hydrate which was only slowly reduced over platinum.

Treatment of the mixture obtained from catalytic reduction with lithium aluminum hydride (equation B) gave a dense semi-solid oil which could be crystallized only from paraffin solvents. The crystalline product thus obtained generally exhibited very wide melting point ranges and uninterpretable nmr spectra. The infrared spectra (e.g., Fig. 8) exhibited both free and hydrogen bonded hydroxyl peaks. No carbonyl function was observed. The ultraviolet spectra exhibited well-resolved benzenoid bands of constant wavelength but generally of irreproducible extinction coefficients.

The enol acetate (19) was reduced to 27 over Adams catalyst (equation C), and the product was treated with lithium
Fig. 8. Infrared Spectrum (CHCl₃) of Reduction Product 16
aluminum hydride. The product was quite similar to that obtained by route 9 and also could be crystallized only from paraffin solvents. Although the melting range was somewhat different, it was still wide. The infrared spectra were identical to Fig. 8.

The reduction product obtained via equation C gave better nmr spectra, but, unless great care was taken to dry it carefully at moderate temperatures, it showed strong signals between 0.0-1.0 ppm from solvent. The sample, purified and dried in this manner, did not give acceptable elemental analyses. Samples dried at temperatures greater than 80° appeared to decompose.

1-Methyl-3-benzal-4-piperidinol (28) (Equation D)

Reduction of 15a with lithium aluminum hydride gave a crystalline product which was shown to be consistent with structure 28. This substance, recrystallized from ligroin, was a white solid melting between 67-119°. The nmr spectrum again showed well-resolved solvent peaks between 0-1 ppm. As with alcohol 16, attempted drying at elevated temperatures led to apparent decomposition. However, a sample dried by heating the molten substance well above the melting point for several minutes gave a sharp melting point, the nmr spectrum gave a good integration, and the ultraviolet spectrum was entirely consistent with the styrene chromophore present. It is now felt that both alcohols, 16 and 28, trap or "include" solvents when recrystallized from hydrocarbon solvents. Loss of these solvents accounts for the apparent decomposition.
observed on heating.

**Attempted Cyclization of Alcohol 16 to Form 17**

Several attempts were made to cyclize the saturated alcohol 16 using the conditions described by Cook and Hewett. Modifications of temperature and reaction time were employed, and polyphosphoric acid was utilized as a catalyst, under varying reaction conditions. In every case, only dehydration products could be isolated:

![Reaction Scheme]

This was rather disappointing, but, in retrospect, not too surprising. None of the alcohols (11, 12, and 13) which underwent cyclization bore the hydroxyl group on the carbon atom which ultimately formed the new bond to the phenyl. Hence, it is obvious that the attacking carbonium ion, or carbonium ion-like species, must migrate around the ring until it is located on a carbon atom which can give electrophilic attack on the phenyl to form a six-membered ring, rather than a three-, four-, or five-membered ring.
In the case of the piperidinol 16, the presence of the basic nitrogen would hinder carbonium ion formation due to ammonium ion formation with the Lewis acid catalyst.
A carbonium ion formed in the same ring would be destabilized by this ammonium ion and probably would not exist long enough to migrate to another position even closer to the nitrogen. Hence elimination of a proton would occur more rapidly than rearrangement and cyclization; reformation of a new carbonium ion would be less likely to occur, and, therefore, only olefin would be isolated.

The Mannich Condensation

In 1962 House, Wickham, and Muller described the preparation of bicyclo keto-amines (29) via the Mannich condensation:

\[
\begin{align*}
0 &= \text{CH}_2\text{N}_2\text{H}_2 \cdot \text{HCl} + 2 \text{CH}_2\text{O} \rightarrow \\
& \quad \text{HOAc} \quad 100^\circ \\
& \quad \text{CH}_2\text{O}_n\text{N}-\text{CH}_3 \\
& \quad n=2,3,4
\end{align*}
\]

Although the reported yields were low (6-13%), this reaction would provide a one step synthesis from 6-tetralone (30) of 3-methyl-6,7-benzo-3-azabicyclo[3,3,1]nonen-9-one (31), which could be reduced to the desired bicyclic amine 17.

\[
\begin{align*}
\text{30} + \text{CH}_3\text{NH}_2 \cdot \text{HCl} + 2 \text{CH}_2\text{O} & \rightarrow \\
& \quad \text{31}
\end{align*}
\]
Preparation of ketone 31 offered several advantages over the direct preparation of the parent compound 17. The racemic substance could be resolved and the ord and cd spectra determined. After the absolute configuration had been determined by application of the octant rule to the Cotton effect given by the carbonyl group, the optically active substance could be reduced to optically active 17, followed by determination of the ord and cd spectra. Since the absolute configuration would be known, this would provide an excellent model for a sector rule for the phenyl chromophore. If compounds bearing substituents on the phenyl ring were prepared, the effect of these substituents on the ord and cd spectra could be compared. The carbonyl group, one of the most useful functional groups, would undergo reaction with a variety of reagents to give a large number of derivatives.

β-Tetralone itself is an expensive, commercially available material, but the number of derivatives is limited. It was hoped that a general method of preparing substituted 2-tetralones could be found in order to introduce substituents into the aromatic ring.

The commonly used method of β-tetralone preparation, the Birch reduction of alkyl 2-naphthyl ethers,28 appeared to be somewhat restricted in its synthetic scope,
However, a Friedel-Crafts reaction reported by Burckhalter and Campbell\textsuperscript{29} appeared to lend itself to formation of a number of derivatives of \textbf{30}. A large number of phenylacetic acids and the remainder of the necessary reagents are readily accessible.

\[
\text{COCl} + \text{CH}_2\text{CH}_2 \xrightarrow{\text{AlCl}_3} \text{C}_5\text{H}_4 \xrightarrow{\text{"drop-in"}} \text{AlCl}_3 \to \text{30}
\]

One disadvantage of the scheme soon became evident: even with the use of the drop-in technique, the reaction must be run in large volumes of solvent to diminish the polymerization of the reagents. Considerable amounts of intractible tars are formed from polymerization of ethylene, making product purification difficult.

Although the method may be useful for preparing some otherwise unavailable 2-tetralones, it was found that the Birch reduction\textsuperscript{28} is a much more facile reaction. The use of the bisulfite adduct as a tool for purification of 2-tetralones cannot be overemphasized.

Preliminary investigations of the Mannich cyclization gave as product large amounts of polymeric material and small amounts of an amine which behaved as though it were the expected product \textbf{31}. House and co-workers\textsuperscript{27} reported the formation of relatively large amounts of dimeric material (\textbf{32}), which could be separated from the desired product only with
difficulty.

Resonance stabilization renders the benzylic α-protons of β-tetralone more acidic and, therefore, more reactive than those at C-3. Reaction at this site alone would produce 33 rather than the desired product 31.

It was found that slow addition of β-tetralone to the reaction mixture via drop-in technique substantially increased the yield of 31. The amount of polymeric material was decreased if the reaction time were shortened. Optimum conditions were obtained when heating was halted only 5-10 minutes after the β-tetralone had been added. An aliquot removed at this point gave a light tan precipitate when neutralized with dilute base, and the "β-tetralone blue test" gave no
color. Continued heating produced decomposition of the product.

With these modifications, substantially improved yields (39-56%) of crude product were obtained. Purification was made difficult by the presence of polymeric material and other by-products such as 33. Most of the polymeric substances were removed by treatment with activated charcoal followed by passing the substance through a short column of alumina or Florisil. The crude product was recrystallized from methanol to give 31, and the infrared (Fig. 9) and nmr spectra (Fig. 10) were consistent with this assignment of structure.

Attempted reduction of the ketone (31) to 17 according to the following scheme was unsuccessful, possibly because the formation of the tosylate was sterically hindered. No further reactions were attempted on 31.

\[
\begin{align*}
31 & \xrightarrow{\text{LiAlH}_4} \text{OH} \\
& \xrightarrow{\text{TsCl}} \text{N} \xrightarrow{\text{CH}_3} \\
& \text{LAH} \xrightarrow{\text{TosCl}} 17
\end{align*}
\]

**Attempted Preparation of 2'-Methoxy-3-methyl-6,7-benzo-3-azabicyclo[3,3,1]nonen-9-one (34)**

Since all of the benzomorphans (7) prepared by May and co-workers contain a 2'-oxy substituent, it was desirable
Fig. 9. Infrared Spectrum (CHCl₃) of 31
Fig. 10. NMR Spectrum (CDCl$_3$) of 31
to attempt the preparation of 34, using as starting material 35.

The methoxy substituent of 35 would decrease the relative acidity of the benzylic protons due to inductive effects, and the resonance stabilization of the enolate anion would be correspondingly decreased:

Rather than being detrimental to the formation of 35, it was felt that, if the relative acidities of the protons at C-1 and C-3 were more nearly equivalent, the probability of cyclization would be enhanced and the possibility of formation of the dimeric-type product would be decreased.

6-Methoxy-2-tetralone (35) was prepared via the
Friedel-Crafts cyclization of p-methoxyphenylacetyl chloride in poor yields. It was subjected to the same Mannich reaction conditions as 30, but no characterizable products were isolated. However, the Mannich condensation holds promise for preparation of derivatives of this type, and further investigation is warranted.

Resolution of 3-Methyl-6,7-benzo-3-azabicyclo[3,3,1]nonen-9-one (31)

The choice of proper resolving agents would appear to be more dependent on fortune than science. Attempted resolution with (+)-camphor-10-sulfonic acid gave a crystalline salt which precipitated as an intractible oil from all solvents on attempted recrystallization. The (+)-tartrate, however, precipitated from acetone as a tan crystalline solid and could be readily recrystallized. The first fraction to precipitate from solution was enriched with the (-)-isomer. Two recrystallizations from an ethanol-acetone solvent, followed by regeneration of the free base, gave levorotatory 31.

The (+)-isomer was isolated from the crop of precipitate which exhibited the largest rotations by repeatedly extracting the more soluble (+)-diastereomer from the solid with boiling acetone. Following recrystallization from acetone and regeneration of the free base, there was obtained (+)-31, which gave rotations of nearly twice the magnitude of the (-)-isomer.

A plausible explanation for the small rotations of
the (-)-isomer is that by changing to a mixed solvent system
the relative solubilities were changed. The pure (-)-isomer
remained in solution allowing the racemic material to crystall­
lize first, carrying some levo-isomer with it. It is, of
course, always inadvisable to use mixed solvents for recry­
stallizations, or to change solvent systems during a resolu­
tion, but such action was deemed necessary.

The infrared spectra of both enantiomers were identical
to that of the racemic material.

Electronic Spectra of 3-Methyl-6,7-benzo-3-azabicyclo[3,3.1]­
nonen-9-one (31)

The ultraviolet spectrum of 31 is complex (Fig. 11),
and the intensities of the absorption bands are strongly
dependent on both concentration and solvent. The molar
extinction coefficients generally decrease with increasing
polarity of the solvent. The spectra exhibit the expected
benzenoid π→π* transition (B_2u ← A_{1g})^{31} near 270 nm with
molar extinction coefficients ranging from 560 in dilute
hydrochloric acid to 1620 in EPA. The absorption near 230
nm probably represents the so-called "K" band or first
primary band (B_{1u} ← A_{1g})^{31} of the phenyl group. The inten­sity also varies with solvent, ranging from 5000 in basic
methanol to 13000 in acidic methanol solution. Hence this
band, unlike the longer wavelength bands, appears to increase
in intensity with increased solvent polarity. The amine
would be expected to absorb in the 200-220 nm region
(ε 1000),^{32} but the low intensity would result in its
Fig. 11. UV Spectra of 31 in Various Solvents

- Dilute HCl
- EPA
- Basic methanol (c=1.7x10^-3)
- Basic methanol (c=3.4x10^-4)
being obscured by the stronger benzene bands. Since no bands appear to diminish in intensity or disappear in acidic medium, it is assumed that this band is not observed. An intense band observed near 195 nm (ε 21000) in water probably represents the second primary band (E20 ← A10) of the phenyl group.31

The carbonyl function is expected to show a weak n → π* transition near 300 nm, and bands in this region are observed, although of greatly enhanced intensity. It has been reported that β,γ-unsaturated ketones frequently exhibit carbonyl n → π* absorption bands of intensity greatly increased over those of isolated ketones.33 This may result from "homoconjugation" through space of the ketone with the π system of the aromatic ring. This has been described as a donation of intensity of the phenyl π system to the n → π* transition of the carbonyl group, resulting in great enhancement of the intensity of this band.34 Cookson and Wariyar35 have reported that this type of electronic interaction occurs in a large number of homoconjugated phenyl ketones which meet certain geometric conditions. Specifically, the unoccupied p orbital of the carbonyl carbon must be pointed directly toward a pπ orbital of a double bond or aromatic ring. In the case of parasantonide (36), which exhibits an unusually strong absorption band in ethanol near 300 nm (ε 1170)35 the ring system is highly strained, causing the carbonyl group to come within rather close proximity of the double bond, allowing a large amount of orbital overlap.
On the other hand, 31 is nearly free of ring strain and it is not obvious that the carbonyl carbon is well aligned to give as effective overlapping of orbitals. It might therefore be expected to show less enhancement of the n → π* transition. However, Cookson and Wariyar35 state that molar extinction coefficients of 300-1000 are indicative of homoconjugated β,γ-unsaturated ketones; and since 31 exhibits bands of similar intensities near 300 nm (ε 600) in EPA and basic methanol, the orbital overlap must be quite efficient; a large n → π* Cotton effect should be observed in this region. 34 It is also apparent that the intensity of the band is quite sensitive to solvent and concentration, changing in intensity by nearly a factor of ten between dilute acid and EPA, the latter giving the higher value.

Optical Rotatory Dispersion and Circular Dichroism Spectra of 31

The ord and cd spectra of 31 are very interesting. The most prominent Cotton effect in EPA (Fig. 12) results from the homoconjugated n → π* transition of the carbonyl
Fig. 12. ORD and CD Spectra of 31 in EPA
group near 300 nm as expected from the ultraviolet spectrum. The ord spectra of both isomers exhibit first extrema near 320 nm, reversal of sign near 300 nm, and second extrema at 282 nm. The curves give a mirror image relationship. (It is apparent that the (−)-isomer is only about one third as optically pure as the (+)-isomer, but since it is not known whether the latter is optically pure, no corrections to "optical purity" have been made.) Hence it appears that the D-line rotations are under the influence of this Cotton effect, and reversal of sign does not occur between the D-line and the first extremum; the (+)-isomer gives a positive Cotton effect at 300 nm. The cd spectrum of (+)-31 shows a (+)-Cotton effect with fine structure of maximum ellipticity at 303 nm, and a (−)-Cotton effect at 275 nm. This second Cotton effect almost certainly arises from the $B_{2u} \rightarrow A_{1g}$ transition of benzene, which appears at 270 nm in the ultraviolet spectrum. The broad trough in the ord spectrum represents not only the second extremum of the Cotton effect at 300 nm but also the first extremum of a negative Cotton effect at 270 nm. Both spectra indicate the beginning of a second positive Cotton effect below 250 nm, which would be caused by the $B_{1u} \rightarrow A_{1g}$ band near 230 nm.

Attempts to obtain both the ord and cd spectra of (+)- and (−)-31 in acidic methanol were disappointing. The $n \rightarrow \pi^*$ band of the carbonyl group was either not present or beyond the limits of detection. The two benzene transitions could be observed only under optimum experimental
conditions in the cd spectrum of the (+)-isomer as very weak bands, \([\theta]_{275} -70^\circ\) and \([\theta]_{232} -600^\circ\). In dilute hydrochloric acid a similar phenomenon occurred, and only one band of moderate intensity could be seen at 222 nm, \([\theta]_{\text{max}} -1400^\circ\).

When the methanolic solution was basified, however, the \(n \rightarrow \pi^*\) band reappeared, and the Cotton effect at 300 nm could easily be measured in both the cd and ord modes (Figs. 13, 14). Dilution of the sample by one-fifth did not give the expected ellipticities and rotations of one-fifth intensity, but, again, the band at 300 nm seemed to disappear. The benzene transitions were measurable and gave values similar to those obtained in EPA solution.

Loss of the ketone \(n \rightarrow \pi^*\) Cotton effect can be explained by hemiketal and ketal formation in acidic and, apparently to a lesser extent, in basic methanolic media.

Reduction in the amplitude of the \(B_{2u} \leftarrow A_{1g}\) transition in acidic media can be explained due to loss of homoconjugation with the ketone group which is apparently no longer present due to ketal formation. It has been reported that the benzenoid transition of the homoconjugated ketone 37 is of normal intensity in the ultraviolet, but is enhanced to a great extent in the cd (\([\theta]_{274} -11000^\circ\)). On the other hand, the alcohol 38 demonstrates no observable Cotton effect for the \(B_{2u} \leftarrow A_{1g}\) transition.\(^\text{36}\)

\[37\]
\[38\]
Fig. 13. CD Spectrum of 31 in Basic Methanol
Fig. 14. ORD Spectrum of 31 in Basic Methanol
The magnitude of the ellipticity of 31 deserves some comment. A number of β-phenyl ketones have been examined by ord and cd and have been shown to have ellipticities in the order of 10,000° to 100,000°.\(^{37,38}\) It is apparent that the angle made by the carbonyl and aryl groups is critical for maximum orbital interaction. This suggests that the enantiomeric 31 isomers (a) are optically impure (or, more accurately, slightly resolved), (b) have poor interaction of the orbitals, or (c) are showing non-interpretable results because of a "double-humped" curve,\(^ {39}\) or some other phenomenon. In view of the exaltation of the uv absorption, (b) does not seem plausible. On the other hand, Dreiding models of 31 compared with compounds of exceptional electronic interaction such as parasantonide (36) show an angular distortion that suggests that the interaction is much smaller.

A number of ketones have been shown to exhibit cd curves in which two maxima are displaced from the normal absorption wave lengths because of a mathematical balancing of two close maxima of opposite sign. Examples include such molecules of free conformation as menthone (39), a number of steroids having the carbonyl group in the more flexible A-ring and some very rigid bicyclic ketones such as isofenchone (40). Explanation for this phenomenon in these terpenes was based on the asymmetric solvation of the chromophore. This could also explain the double-humped curve of 31 since the rigidity of the molecule precludes a conformational equilibrium.\(^ {40}\) It leaves open the question of orbital
interaction since no attempt at variable temperature cd was made.

\[
\text{Fig. 15. Sector Rule for } \beta,\gamma\text{-Unsaturated Ketones}\]

Application of the Octant Rule to 31 for Determination of the Absolute Configuration

The octant rule for ketones has been extended to include \(\beta,\gamma\)-unsaturated ketones. Since the homoconjugated system is considered to be a dissymmetric chromophore, the following pictorial sector rule has been suggested.

\[
\text{Fig. 15. Sector Rule for } \beta,\gamma\text{-Unsaturated Ketones}^41
\]
The configuration of the left (A) would be expected to give a (-)-Cotton effect while that on the right (B) would exhibit a (+)-Cotton effect. Application of this to 31 is summarized in Fig. 16.

Fig. 16. β,γ-Unsaturated Ketone Rule Applied to 31

The isomer which corresponds to B would give a (+)-Cotton effect near 300 nm and has the absolute configuration of the asymmetric bridgehead carbon atoms 1R, 5S, and is therefore designated as (+)-(1R;5S)-3-methyl-6,7-benzo-3-azabicyclo[3.3.1]nonen-9-one.

The mirror image isomer (Fig. 16A) has the absolute configuration of the asymmetric atoms 1S and 5R and is therefore (-)-(1S;5R)-31.
The 6,7-Benzomorphans (7)

The benzomorphans (7a-7g) were supplied in 97-100% optical purity, and bear the following structures:

\[
\begin{align*}
7a & \quad \alpha(-), \text{R}=\text{R}'=\text{CH}_3, \text{R}''=\text{H} \\
7b & \quad \beta(-), \text{R}=\text{R}'=\text{CH}_3, \text{R}''=\text{H} \\
7c & \quad \alpha(-), \text{R}=\text{R}'=\text{R}''=\text{CH}_3 \\
7d & \quad \alpha(+\text{ and } -), \text{R}=\text{CH}_3, \text{R}'=\text{CH}_2\text{CH}_3, \text{R}''=\text{H} \\
7e & \quad \beta(-), \text{R}=\text{CH}_3, \text{R}'=\text{CH}_2\text{CH}_3, \text{R}''=\text{H} \\
7f & \quad \alpha(-), \text{R}=\text{CH}_2\text{CH}_2\text{Ø}, \text{R}'=\text{CH}_3, \text{R}''=\text{H} \\
7g & \quad \alpha(+\text{ and } -), \text{R}=\text{CH}_2\text{CH}_2\text{Ø}, \text{R}'=\text{R}''=\text{CH}_3 \\
7h & \quad (-), \text{R}=\text{R}''=\text{H}, \text{R}'=\text{CH}_2\text{CH}_3 (\text{The configuration at position 9 is unknown.})
\end{align*}
\]

Ultraviolet Spectra of 7

The ultraviolet spectra (methanol) of all derivatives of 7 exhibit two major bands. The long wavelength band, appearing between 280-290 nm (ε 2200-2500), represents the $B_{2u}\leftarrow A_{1g}$ transition of the benzene, and appears to remain unchanged upon converting free bases to hydrochlorides and hydrobromides to free bases (e.g., Fig. 17). All the compounds exhibit some indication of fine structure which is more
Fig. 17. UV Spectra of 7a in Methanol as Free Base and Hydrochloride
pronounced in the compounds with methoxy substituents (7c, 7g). Additional fine structure can be seen in the spectra of the phenethyl derivatives (7f, 7g), no doubt a contribution of the second phenyl group, but the molar extinction coefficients are not detectably changed.

A second transition can be seen near 220-230 nm (ε 5500-6500) and usually appears as two shoulders on a larger background curve. In this case, the bands are usually more distinct for the hydrohalide salts than for the free bases. This transition would represent the first primary band (\( R_{1u} \leftarrow A_{1u} \)) of the phenyl. The fact that the band does not disappear or diminish in acidic solution indicates that it is not the \( n \rightarrow \sigma^* \) transition of the amine. The third band which reaches a maximum below 200 nm is of large intensity and could not be measured. It probably represents the second primary band (\( E_{1u} \leftarrow A_{1g} \)) of the phenyl group, which would be expected to appear at about 190 nm.

Optical Rotatory Dispersion and Circular Dichroism Spectra of the 6,7-Benzomorphans (7)

The ORD spectra of these compounds are rather complex, and interpretation is difficult. In each case the first extremum appears between 290-295 nm and the second appears around 270 nm; the Cotton effect may exhibit reversal of sign, but it is never symmetrically disposed about the zero line (e.g., Fig. 18). Fine structure may be seen in some of the curves, again being more pronounced in the methoxy derivatives. The amplitude is decreased in the free base relative to the hydrohalide salt, but this is largely due to concurrent changes
Fig. 18. ORD, CD and UV Spectra of 7c•HBr in Methanol
in the intensities of lower wave length bands. The amplitudes of the hydrohalide salts range from 50-55 and for the free bases from 40-45.

It is apparent that a second Cotton effect, generally of opposite sign to that at long wave length, exists in the region of the 225 nm band in the ultraviolet, and appears to vary considerably in amplitude and shape between the free bases and the salts (Fig. 19).

The cd spectra, in all cases, exhibit a band near 290 nm, corresponding to the $B_{2u} \leftrightarrow A_{1g}$ transition, and a second band near 225 nm, corresponding to the $B_{1u} \leftrightarrow A_{1g}$ transition (Fig. 20). With the exception of the phenethyl derivatives, 7f and 7g, as the free bases, the two transitions are of opposite sign. Such opposition of sign of the two bands has been reported for a number of aromatic compounds and is considered "normal".\(^\text{42}\) As in the ultraviolet and ord spectra, the long wave length band appears nearly unchanged between the free bases and the hydrohalide salts (Fig. 20). In fact, only two compounds, 7c and 7e, exhibit a difference in amplitude of as much as 10 percent in comparing the salt to the free base, and the ellipticity values of the entire series are quite similar to one another (Table 1). The lowest ellipticities occur when fine structure is more pronounced (i.e., more separation). The intensities of the individual separated bands would be smaller than the resulting summation of overlapping bands.\(^\text{43}\)
Fig. 19. ORD Spectra of 7a as Free Base and Hydrochloride
Fig. 20. CD Spectra of (+)-7d as Free Base and Hydrochloride
## Table 1

$B_{2u} \leftarrow A_{1g}$ Cotton Effect of the 6,7-Benzomorphans (7)

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\lambda_{max}$ (nm)</th>
<th>$[\theta]_{max}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>(-)-7a (base)</td>
<td>282</td>
<td>$-4500^\circ$</td>
</tr>
<tr>
<td>(HCl)</td>
<td>281</td>
<td>$-4800^\circ$</td>
</tr>
<tr>
<td>(-)-7b (base)</td>
<td>284</td>
<td>$-3600^\circ$</td>
</tr>
<tr>
<td>(HBr)</td>
<td>285</td>
<td>$-3750^\circ$</td>
</tr>
<tr>
<td>(-)-7c (base)</td>
<td>283</td>
<td>$-5000^\circ$</td>
</tr>
<tr>
<td>(HBr)</td>
<td>287, 278</td>
<td>$-3900^\circ$, $-4100^\circ$</td>
</tr>
<tr>
<td>(+)-7d (base)</td>
<td>283</td>
<td>$+3900^\circ$</td>
</tr>
<tr>
<td>(HCl)</td>
<td>283</td>
<td>$-3750^\circ$</td>
</tr>
<tr>
<td>(-)-7d (base)</td>
<td>283</td>
<td>$-3900^\circ$</td>
</tr>
<tr>
<td>(HCl)</td>
<td>283</td>
<td>$-3750^\circ$</td>
</tr>
<tr>
<td>(-)-7e (base)</td>
<td>285</td>
<td>$-3900^\circ$</td>
</tr>
<tr>
<td>(HCl)</td>
<td>283</td>
<td>$-4700^\circ$</td>
</tr>
<tr>
<td>(-)-7f (base)</td>
<td>289, 281</td>
<td>$-3400^\circ$, $-3900^\circ$</td>
</tr>
<tr>
<td>(HBr)</td>
<td>282</td>
<td>$-3900^\circ$, $-3900^\circ$</td>
</tr>
<tr>
<td>(+)-7g (base)</td>
<td>287.5, 281</td>
<td>$+3100^\circ$, $+3900^\circ$</td>
</tr>
<tr>
<td>(HBr)</td>
<td>288, 279</td>
<td>$+3500^\circ$, $+3700^\circ$</td>
</tr>
<tr>
<td>(-)-7g (base)</td>
<td>288, 280</td>
<td>$-3600^\circ$, $-4000^\circ$</td>
</tr>
<tr>
<td>(HBr)</td>
<td>287.5, 279.5</td>
<td>$-3900^\circ$, $-4150^\circ$</td>
</tr>
<tr>
<td>(-)-7h (base)</td>
<td>285</td>
<td>$-3600^\circ$</td>
</tr>
<tr>
<td>(HCl)</td>
<td>284</td>
<td>$-3550^\circ$</td>
</tr>
</tbody>
</table>
Since these values are nearly invariable, the data will be treated in this manner rather than attempting to interpret small and subtle changes.

The Cotton effect which appears near 225 nm is much more variable. As a rule, the hydrohalide salts give $[\Theta]_{\text{max}}$ values which are two to four times larger than those of the free bases (Fig. 21). The hydrohalides of 7a and 7c give the largest Cotton effects ($[\Theta]_{\text{max}}$ 10000 and 11000°) while the phenethyl compounds, 7f and 7g, give the smallest values ($[\Theta]_{\text{max}}$ 3300 and 5000°). For the free bases, the range of values is somewhat smaller, but again, 7a and 7c give the largest values ($[\Theta]_{\text{max}}$ +5550° and +4100°). The smallest value obtained for a "normal curve" is given by 7d. The smallest difference between the acid and base forms is given by the secondary amine 7h. The data for the 225 nm Cotton effect are summarized in Table 2.

As mentioned before, the β-phenethyl compounds, 7f and 7g, do not exhibit "normal curves" as the free bases (Fig. 22). It is somewhat difficult to ascertain whether the band between 225 and 230 nm, in the spectrum of the base, represents a Cotton effect of abnormal sign or a normal Cotton effect superimposed on a very strong transition near 200 nm. Inspection of the ord spectra of 7f (Fig. 23) leads to the conclusion that the Cotton effect does change sign. The curve of the free base increases in negative value much more rapidly than does that of the hydrobromide, and it appears to give a trough at 236 nm. The salt, however, gives an inflection
Fig. 21. CD Spectra of 7e as Free Base and Hydrochloride
### Table 2

$\text{R}_{lu} \rightleftharpoons \text{A}_\text{Lq}$ Cotton Effect of the 6,7-Benzomorphans (\( \gamma \))

<table>
<thead>
<tr>
<th>Compound</th>
<th>( \lambda_{\text{max}} )</th>
<th>( [\theta]_{\text{max}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>(-)-7a (base)</td>
<td>228</td>
<td>+5550°</td>
</tr>
<tr>
<td>(HCl)</td>
<td>227.5</td>
<td>+11000°</td>
</tr>
<tr>
<td>(-)-7b (base)</td>
<td>227</td>
<td>+3000°</td>
</tr>
<tr>
<td>(HBr)</td>
<td>228</td>
<td>+8100°</td>
</tr>
<tr>
<td>(-)-7c (base)</td>
<td>226</td>
<td>+4100°</td>
</tr>
<tr>
<td>(HBr)</td>
<td>228</td>
<td>+10000°</td>
</tr>
<tr>
<td>(+)-7d (base)</td>
<td>230</td>
<td>-1750°</td>
</tr>
<tr>
<td>(HCl)</td>
<td>232, 228</td>
<td>-5900°, -6300°</td>
</tr>
<tr>
<td>(-)-7d (base)</td>
<td>ca. 228</td>
<td>+1200°</td>
</tr>
<tr>
<td>(HCl)</td>
<td>229</td>
<td>+4700°</td>
</tr>
<tr>
<td>(-)-7e (base)</td>
<td>227</td>
<td>+2800°</td>
</tr>
<tr>
<td>(HCl)</td>
<td>228</td>
<td>+8200°</td>
</tr>
<tr>
<td>(-)-7f (base)</td>
<td>231 (225)</td>
<td>-2900° (-1800°)</td>
</tr>
<tr>
<td>(HBr)</td>
<td>228</td>
<td>+4900°</td>
</tr>
<tr>
<td>(+)-7g (base)</td>
<td>228 (227)</td>
<td>+4800° (+4400°)</td>
</tr>
<tr>
<td>(HBr)</td>
<td>231</td>
<td>-4100°</td>
</tr>
<tr>
<td>(-)-7g (base)</td>
<td>231 (225)</td>
<td>-5800° (-5600°)</td>
</tr>
<tr>
<td>(HBr)</td>
<td>229</td>
<td>+3300°</td>
</tr>
<tr>
<td>(-)-7h (base)</td>
<td>229</td>
<td>+3900°</td>
</tr>
<tr>
<td>(HCl)</td>
<td>229</td>
<td>+5000°</td>
</tr>
</tbody>
</table>
Fig. 22. CD Spectra of 7f as Free Base and Hydrobromide
Fig. 23. ORD Spectra of 7f as Free Base and Hydrobromide
for a peak between 245 and 250 nm. In similar systems it has been suggested that the reversal of sign in basic media results from converting the phenol to the phenoxide anion.\textsuperscript{44} This is obviously not the case here; dilute ammonia is not a sufficiently strong base to ionize the phenol and only the phenethyl compounds exhibit this phenomenon, one of which bears a methoxy group. Other phenols in this series do not exhibit this reversal.

**Low Wave Length (E_{1u} \leftarrow A_{1g}) Transition of 7b**

The ord and cd spectra of 7b·HBr (Fig. 24), determined in aqueous solution, exhibit an intense Cotton effect near 190 nm arising from the $E_{1u} \leftarrow A_{1g}$ transition. The band in the cd appears as a doublet, which was reproducible in three separate determinations of the spectrum. The nature of the two weak transitions in the 200-210 nm region is unknown. It is apparent that the observed dissymmetry of the long wave length Cotton effects about the zero line in the ord is due to the influence of this transition.

Recently the ord spectra have been reported for 7a and 7b as the free bases, hydrobromides, and methiodides.\textsuperscript{45} Generally good agreement is found as to position of peaks and troughs, but a disparity of a power of ten in rotational values is observed, the results reported here being the lower. The values of the D-line rotations, measured from the ord spectra, in no case differ by more than 25 percent from the literature values. (Appendix). Solvent effects and use of a different instrument cannot account for the 10-fold
Fig. 24. ORD and CD Spectra of 7b-HBr in H2O

[Diagram showing ORD and CD spectra with wavelength (nm) on the x-axis (180 to 240) and [g]x10^-3 on the y-axis (-60 to 10).]
discrepancy. Although rotations may exhibit a strong dependency on solvent, only negligible differences were seen in the spectra of 7b in water and in methanol. Values of ord amplitude determined on the Cary 60 and the Rudolph instrument generally differ only by 10-15%. The reported assignment of the inflection near 240-250 nm in the ord as a peak is in error. The cd spectra unequivocally demonstrate that this is not the beginning of the 230 Cotton effect, since no ellipticity is observed in this region.

**Determination of Absolute Configuration and Development of a Sector Rule**

It is evident from the data provided by the series of benzomorphans that postulation of a sector rule for determination of their relative configurations is unnecessary. Knowledge of the sign of the first Cotton effect (280 nm) is sufficient. However, since in no case does the sign of this differ from the sign of the rotation at the D-line, a knowledge of the latter might suffice in predicting the relative configuration. The compounds contain three asymmetric carbon atoms, and the relative configurations at C1 and C5 are easily determined from the general shape of either the ord or cd curves. No such simple observation can be applied for prediction of the configuration at position 9.

The absolute configuration of (-)-7d is known to be 1R,5R,9R since it has been prepared \textit{via} degradation of thebaine (3). All the (-)-derivatives of 7 bear the same 1R,5R configuration; (-)-α-derivatives are 9R and (-)-β-
derivatives are 95. The opposite configurations will be present in enantiomeric forms.

On the one hand, it might appear that the lack of significant change in the 280 nm Cotton effect due to substituent variations would thwart efforts to postulate a sector rule for the phenyl chromophore. It might also be possible that these data define a rigid set of conditions according to which a sector rule could be formulated.

It can be assumed that the nitrogen atom and substituents thereon make minor contributions to the perturbation of the aromatic ring. The presence and nature of substituents at the 5 and 9 positions seem to bear little import. It has been reported that the configuration at C9 is unimportant,45 and this seems to be the case.

Previous workers have attempted to define an "octant rule" for benzene identical to the highly successful rule for ketones.12,13 It is not obvious that such a rule is possible for a chromophore of such great complexity. In the case of cyclohexanones, the sector rule is based on the symmetry of the ground and the \( \pi^* \) states,10 and this can logically be extended to form the octant rule.

Benzene, however, exhibits two electronic transitions in the ultraviolet spectrum above 200 nm. The lowest lying unoccupied \( \pi \) orbitals are the degenerate antibonding \( \pi_4 \) and \( \pi_5 \) orbitals, designated as \( \pi^* \). As an additional complication, the highest occupied \( \pi \) orbitals, \( \pi_2 \) and \( \pi_3 \), are also degenerate, indicating that the ultraviolet spectral bands could
arise from any one of four possible transitions.\textsuperscript{47}

Both the $\pi_4$ and $\pi_5$ orbitals contain two out of ring nodal planes. The ring itself is in a third plane, and nodes behind the ring are of opposite sign to those in front (Fig. 25). The $\pi_4$ orbital may be viewed as eight sections of equivalent volume; this is not possible for $\pi_5$.

\begin{center}
\begin{tikzpicture}
\node at (0,0) {A};
\draw[thick] (0,0) -- (1,1) -- (2,0) -- (1,-1) -- cycle;
\draw[thick, fill=white] (2,0) -- (2.5,0) -- (2.5,0.5) -- (2,0.5) -- cycle;
\node at (4,0) {B};
\draw[thick] (4,0) -- (5,1) -- (6,0) -- (5,-1) -- cycle;
\node at (8,0) {C};
\draw[thick] (8,0) -- (7,1) -- (6,0) -- (7,-1) -- cycle;
\end{tikzpicture}
\end{center}

$\pi_4$ and $\pi_5$

Fig. 25. Nodal Planes in the $\pi_4$ ((A), along z axis above plane, (B) along y axis) and $\pi_5$ Orbitals of Benzene

If $\pi_4$ is the excited state involved in either of the phenyl $\pi \rightarrow \pi^*$ transitions under consideration, a sector rule based on quadrants or octants may be possible. Since the location of the nodal planes is difficult to determine in the case of unsymmetrically substituted benzenes, it has been suggested that a view down the axis of highest local (i.e., phenyl) symmetry\textsuperscript{12} or along the axis of greatest polarizability\textsuperscript{13} would suffice.

The 1,2,4-trisubstituted benzomorphans contain only one axis of local symmetry, an $S_2$ axis through the 3', 6 positions into the asymmetric benzylic carbon at position 5.
It would be reasonable to expect the axis of greatest polarizability to lie through the OH or OCH$_3$ group on the ring, ergo the 2',7'-axis. These are discussed below.

**Case I: The 2',7'-axis**

If square coordinates are assigned as one views along the 2',7'-axis (polarizability axis) of a (-)-6,7-benzomorphan in the plane of the ring, the molecule is arranged in the manner depicted in Fig. 26.

![Fig. 26. (-)-Benzomorphan as Viewed Along 2',7'-Axis](image)

It can be seen that this does not meet conditions required for a sector rule describing the $B_{2u} \leftarrow A_{1g}$ transition. All groups lie entirely in the rear octants; the front sectors can be neglected. The configuration at carbon 9 would be important since the 9α substituents lie well into lower right hand quadrant while 9β substituents are directed away from the phenyl ring and near a nodal plane.
The nitrogen lies well into the upper right sector, and would be expected to make a large contribution. Moreover, the contribution of the 5,9-substituents oppose those of the amino group. To be consistent with the data, the two groups in the lower right sector would need to nearly balance the effect of the amine.

**Case II: The 3',6 ‐ axis**

In viewing down the 3',6 ‐ axis (axis of highest local symmetry) the projection of a (-)-benzomorphan is as follows:

![Diagram of (-)-benzomorphan](image)

*Fig. 27. (-)-Benzomorphan as Viewed Along the 3',6 ‐ axis*

Here again the model does not appear consistent with the data. The amino group should make a large contribution if it is able, and the stereochemistry of position 9 would be important, although it is somewhat nearer the vertical nodal plane than in Case I.
Case III: The Axis Between 2'-3' and 6-7

Three axes are needed to define all possible orientations of the phenyl ring. (Others represent either 90° or 180° rotations, and would be redundant.) The third necessary axis can be the axis bisecting the 2'-3' and 6-7 bonds, called the midway axis.

Fig. 28. (-)-Benzomorphan as Viewed Along Midway Axis

Of the three possibilities, this appeared to be most nearly consistent with the data. The 9-position is quite near a nodal plane, as is the nitrogen atom, and the contributions of an α-substituent should be small. The configuration of position 9 would make small, and perhaps undetectable, differences. In all three projections the substituents on the asymmetric benzylic carbon atom (C₅), which in fact determines the geometry of the entire ring system, would be important, and in each case the nature of R' on that atom
may, or may not, make a measurable contribution. If the back octants of the projection along the midway axis are signed as follows, a sector rule is obtained which is consistent with the data.

\[ \begin{array}{cc}
- & + \\
+ & - 
\end{array} \]

If the contribution of the methylene groups \((C_3\) and \(C_4)\) which are projected into the upper right rear octant do not dominate the sign of the Cotton effect (i.e., make major contributions), the sector rule is consistent with the spectra given by the 6,7-benzomorphans. Examination of the reported ord and cd spectra of several morphinan (6) and morphine derivatives confirms the validity of this assumption.

Levorphanol (41) is a simple morphinan, differing from the 6,7-benzomorphane 7d only in that the 5,9-diethyl substituents are joined, forming a fourth ring.
Compound 41 gives the projection shown in Fig. 29. The system is strain-free and the arrangement is identical to that of 7d. However, since the 5,9-diethyl groups are fused into a ring, they cannot move into adjacent octants, and 41, therefore, would be expected to give a somewhat larger (-)-Cotton effect near 280 nm.

![Fig. 29. Projection of 41](image)

The compound exhibits an ord trough at 290 nm and a peak at 268 nm as both the free base and the hydrochloride salt, with amplitudes reported as -566 and -644 respectively. These values are extremely large, but, since they are taken from the same paper in which 7a and 7b were reported, it is probable that the real values are -56.6 and -64.4. These are indeed larger than the corresponding values for 7d as the free base (A=-44) and in acidic methanol (A=-52), indicating that the ethyl groups of 7d are able to go into octants...
of opposite sign.

Compound 42 contains a keto-function which is projected into the lower right far octant (Fig. 30). This should make a significant contribution to the amplitude of the $\mathbb{R}_{2u} \leftrightarrow \mathbb{A}_{1q}$ Cotton effect. The enantiomeric (+)-isomer exhibits a positive Cotton effect in dioxane $(\lambda = +95)^{48}$ which is considerably larger than those of compounds 7d and 41.

![Chemical Structure of Compound 42](image)

Fig. 30. Projection of 42
The deoxy-compounds $43$ and $44$ provide further indication that the configuration at C9 is relatively unimportant to the amplitude of the Cotton effect. Compound $43$ has the 9$\sigma$-configuration, and $44$ has 9$\beta$-configuration.

The projections of the two compounds along the midway axis (Fig. 31) indicate that there should be vanishingly small differences in the Cotton effects given by the two compounds, and in fact the ord spectra are nearly superimposable; compound $43$ exhibits a Cotton effect (methanol) near 275 nm ($\lambda \approx 28$) and $44$ exhibits a Cotton effect in methanol at the same wave length ($\lambda \approx 28$). It is of interest that the lack of the oxygen substituent on the phenyl makes little difference in the shape of the ord spectrum. There is a shift to lower wave length and a decrease in the amplitude. This is also seen in the ultraviolet spectrum: $\lambda_{\text{max}} 275 (\epsilon 800)$. $48$
Extension of the Sector Rule to the Morphine Alkaloids

Since the sector rule involves neither the axis of highest local symmetry (Case II) nor the axis of polarizability (Case I), it was felt that the "rule" might be applicable to the morphines. The morphines differ from the morphinans only by the presence of an ether bridge attached to the aromatic ring at the 1'-position. Examination of Dreiding models indicates that the system is no longer strain-free; considerable torsion is placed on the aromatic ring. The effect of this on the ord and cd spectra is unknown, but it is not unreasonable to expect some effect.
The morphine derivative 45 gives the following projection:

![Diagram of 45]

**Fig. 32. Projection of 45**

The bridgehead carbon atom at position one has been brought down slightly into the lower left quadrant, and the piperidine ring has been skewed to the right so that the nitrogen lies nearly on a nodal plane. The hydroaromatic ring is projected completely into the lower right quadrant. The substance would be predicted to exhibit a negative Cotton effect near 280 nm, but the amplitude is difficult to predict because of ring strain and the presence of the additional phenoxy group. An amplitude of -85 is reported. This is significantly larger than the amplitude of 41 and nearly twice as large as that of 7d, which it closely resembles.

The projection of dihydrocodeine (46), which differs
from 45 by the introduction of an alcohol function, is shown in Fig. 33.

\[
\text{H}_3\text{CO} \quad \text{N-CH}_3
\]

\[
\text{HO}
\]

\[
\text{H}_3\text{C} - \text{N}
\]

\[
\text{HO}
\]

\[
\text{H}
\]

\[
\text{H}
\]

\[
\text{Fig. 33. Projection of Dihydrocodeine (46)}
\]

The hydroxyl group extends under the phenyl ring and should have a significant effect on the Cotton effect. The cd spectrum exhibits a strong Cotton effect at 280 nm with \([\theta]_{\text{max}} = -10550^\circ\text{.} \) Since the amplitude of an ord Cotton effect can be related theoretically to the intensity of the
cd band by the expression \( A = 0.0122 [\theta]_{\text{max}}^{51} \) would give \( A = -130 \). This is a substantial increase over the amplitude of 45.

The methoxy derivative of 46 exhibits an ord Cotton effect of \( A = -110 \), a large enhancement over the value of 45, but somewhat lower than 46 itself.

In codeine (2) a double bond, which would be expected to make an important contribution, is present.

![Fig. 34. Projection of Codeine (2)](image)

The skewing is even more pronounced, and the carbon which corresponds to the 1-position in the benzomorphan may be important since it lies well into the lower left quadrant. The hydroxyl group is no longer directly under the aromatic ring, and its contribution may be diminished. The projection is, therefore, somewhat more difficult to evaluate, although
there can be no doubt that a negative Cotton effect is predicted. In fact, codeine exhibits a (-)-Cotton effect at 282 nm \([\Theta]_{\text{max}} \approx -8600^\circ\),\(^{52}\) indicating that the ring strain which is increased because of the unsaturation produces effects that may counter the effect of the double bond.

Morphine (1) is structurally similar, except that the methoxy group is hydroxyl. Little change in the Cotton effect would be expected. The cd shows \([\Theta]_{293} \approx -7500^\circ\) in acidic methanol.\(^{53}\) A substantial red shift is, however, observed.

Heroin, the diacetate of (1), gives a (-)-Cotton effect at 285 nm, as would be expected, but of greatly reduced intensity, \([\Theta]_{285} \approx -1310^\circ\).\(^{54}\) This has been attributed to the "electron withdrawing properties" of the "acetyl group on the benzene ring."\(^{55}\) In fact the O-acetyl group is electron donating, although to a lesser extent than methoxy and certainly than hydroxyl. It would seem more likely that the contribution of O-acetyl in the lower right quadrant is not the same as hydroxyl or methoxyl.

Thebaine (3) contains a homoconjugated butadiene system which could be expected to dramatically change the Cotton effect. The ring strain is very large, and the phenyl ring must distort from planarity to accommodate this. The nitrogen is brought much nearer the horizontal nodal plane. The butadiene system dominates the projection (fig. 35), but the intensity may be much less than expected if the ring geometry were the same as in the benzomorphinan model. Thebaine
still exhibits the largest Cotton effect of the series; \([\theta]_{285} = 15000^0\). The diene Cotton effect occurs at somewhat lower wave length.\(^{56}\)

![Thebaine Projection](image)

**Fig. 35. Thebaine Projection**

**Extension of the Sector Rule to Other Ring Systems**

Kuriyama *et al.*\(^{12}\) have reported the cd curves of lycoreine (9) and a number of related compounds. They have postulated a sector rule in which one is to view directly down the axis that bisects the methylendioxy ring. These compounds exhibit "weak" Cotton effects in the 290 nm region.

If the system is aligned so that the oxygen atoms are positioned so they lie directly over those of codeine,
the sector rule reported here also gives the correct prediction (Fig. 36).

Fig. 36. Lycorine Projection

Nearly the entire molecule lies in a negative octant, but lycorine is nearly planar and would not be expected to give a large Cotton effect. This is the case: $[\theta]_{289}^{20} -6720^0$.12

This may be fortuitous; other systems also seem to give correlation to the model. The choice of a reference axis, however, appears to be arbitrary and general conclusions are unwarranted at this point.

The sector rule as postulated is consistent with the 6,7-benzomorphans (7), the morphinans (6), and the morphine alkaloids examined.

Reexamination of the 6,7-Benzomorphans (7) and Application of the Sector Rule

Initially the assumption was made that the compounds 7a-7h exhibit Cotton effects near 280 nm which are nearly unaffected by the various substituents present. This is true
when the intensities are compared to values given by the morphinan and morphine series. But the intensities of the Cotton effects are not identical for derivatives of \( \text{7} \), and perhaps these differences can now be interpreted with some degree of sophistication.

Levorphanol (41) exhibits a stronger \( \text{8}_{2u} \rightarrow \text{A}_{1q} \) Cotton effect than does the structurally similar \( \text{7}_{d} \). It has been stated that this may be due to the fact that the 5,9-diethyl substituents are free to pass through nodal planes, giving partly positive contributions to the transition and thereby diminishing the amplitude. It would follow that 5,9-dimethyl substituents should give larger Cotton effects than the 5,9-diethyl compounds. The \( \sigma \)-methyl should make a larger contribution than the \( \beta \)-methyl isomer since it is nearer the aromatic ring.

The observed data give excellent support to this; \( \text{7}_{a} \) and \( \text{7}_{c} \), both bearing 9\( \sigma \)-methyl substituents, give the strongest Cotton effects of the series with ellipticities of nearly 5000°. Compound \( \text{7}_{b} \), with \( \beta \beta \)-configuration gives a substantially weaker Cotton effect (\( \text{[\( \beta \)]}_{\text{max}} 3700° \)).

The intensities of the \( \text{8}_{2u} \rightarrow \text{A}_{1q} \) Cotton effects of the isomeric 5,9-diethyl compounds \( \text{7}_{d} \) and \( \text{7}_{e} \) are identical in the free bases (\( \text{[\( \beta \)]}_{\text{max}} 3900° \)). However, \( \text{7}_{d} \) exhibits almost no change in intensity upon conversion to the hydrochloride while the intensity of \( \text{7}_{e} \) increases by 800°, nearly the largest change in the series. The \( \beta \)-ethyl group can come very near the nitrogen substituent if it also is \( \beta \). This
may explain the increase in amplitude shown by 7e as the hydrochloride; the nitrogen configuration might be different here than in the other compounds in the series.

There probably is contribution from either the nitrogen or its substituents, but it is small. The secondary amine 7h gives nearly identical amplitudes as both the free base and the hydrochloride. With the exception of 7d, the compounds give small changes which cannot be interpreted. The 3-phenethyl compounds, 7f and 7g, give differences of intensity between the hydrobromides and free bases of the same magnitude as other derivatives.

Application of the Sector Rule to 3-Methyl-6,7-benzo-3-aza-bicyclo[3.3.1]nonen-9-one (31)

The projection of (-)-31 along the midway axis is shown in Fig. 37.

Fig. 37. Projection of (-)-31
The only obvious perturbation arises from the carbonyl group. A (-)-Cotton effect would be predicted for the $B_{2u} \rightarrow A_{1q}$ transition, but the isomer shown gives a (+)-Cotton effect near 275 nm. Perhaps the dissymmetry of the system is so small that other factors such as homoconjugation gain in relative importance. It is interesting to note that were the carbonyl group removed, it might be predicted that no $B_{2u} \rightarrow A_{1q}$ Cotton effect would be observed. In acidic methanol solution, where ketal and/or hemiketal formation is important, the amplitude of this Cotton effect nearly vanishes: $[\theta]_{\text{max}} \approx -100^\circ$.

**Sector Rule for $R_{1u} \rightarrow A_{1q}$ Transition of 7**

In the examination of the three possible ways of viewing the aromatic ring, it appeared that Case II (Fig. 27) would describe the Cotton effect at 230 nm arising from the $R_{1u} \rightarrow A_{1q}$ transition. The rear quadrants would be signed as follows:

```
+  -
-  +
```

There is, as before, no way of knowing whether an octant rule is applicable here, but the method has some justification. The amino group of a (-)-6,7-benzomorphan lies well into a (+)-octant, and protonation of the base (forming an ammonium ion) should make a major change. The $9\alpha$-configuration should make a larger contribution than that of $9\beta$. 
Correlation did not appear as good as with the sector rule for the 280 nm band. A complication in attempting to describe the 225 nm band is that it is not isolated from neighboring transitions. The intense $E_{1u} \rightarrow A_{1g}$ transition overlaps and this can be expected to cause significant distortion.

Since this sector rule has been postulated before for the morphine and Amaryllidaceae alkaloids,\textsuperscript{12} it will not be discussed further.
EXPERIMENTAL

General

Melting Points. Melting points were determined with a Hoover capillary melting point apparatus and are corrected.

Analytical Data. Microanalyses were determined on an F and M Model 180 carbon, hydrogen, and nitrogen analyzer, and by Schwarzkopf Microanalytical Laboratory, Woodside, New York.

Infrared Absorption Spectra. The infrared absorption spectra were determined using Models 137 and 337 Perkin-Elmer infracord spectrophotometers. The positions of the absorption bands are given in wave number units, cm⁻¹. The spectra of solids were determined either as mulls in halocarbon oil from 4000 to 1300 cm⁻¹ and in Nujol from 1300 to 650 cm⁻¹ or as solutions in chloroform in matched sodium chloride solution cells of 0.1 mm pathlength. The spectra of liquids were determined as films.

Electronic Absorption Spectra. Electronic absorption spectra were determined on a Cary Model 15 recording spectrophotometer. The positions of absorption bands are given in nanometers, nm. The solvent and concentration (mol/l, solvent) are indicated for each measurement.

Proton Magnetic Resonance Spectra. The proton magnetic resonance spectra were determined with a Varian Model A-60 proton resonance spectrometer. Unless otherwise
indicated, the spectra were obtained in deuterated chloroform; the chemical shifts are given in ppm relative to tetramethylsilane, an internal standard.

**Optical Rotation Data.** Optical rotations were determined on a Carl Zeiss Photoelectric Precision Polarimeter using a mercury vapor lamp as a light source. The specific rotations, $\left[ \alpha \right] (g/100 \text{ml, solvent})$, are given for each measurement.

**Optical Rotatory Dispersion Spectra.** Optical rotatory dispersion curves were determined on either a Cary Model 60 Recording Spectropolarimeter or a Rudolph Recording Spectropolarimeter Model 260/655/850/810-614 in 0.1 dm sample cells. The solvent and initial concentration (mol/100 ml, solvent) are indicated for each curve; data are given as molecular rotations, $[\psi]$.

**Circular Dichroism Spectra.** Circular dichroism spectra were obtained on a Cary Model 6001 Circular Dichroism accessory for the Cary Model 60 Recording Spectropolarimeter. The spectra were determined in a 1.0 cm cell and the initial concentration and solvent (g/cc, solvent) are indicated for each spectrum. Data are given as the molecular ellipticities, $[\psi]$.

The Aldol Condensation of 1-Methyl-4-piperidone and Benzaldehyde

1-Methyl-3-benzal-4-piperidone (15). To a solution of freshly distilled 1-methyl-4-piperidone (261.2 g, 2.3 mol) in 1.5 l of 60% ethanol was added benzaldehyde (250.2 g,
2.35 mol) and potassium hydroxide (92 g, 1.6 mol). The mixture was stirred with the aid of a magnetic stirrer to facilitate dissolution of the base. The solution turned orange immediately, and a red oil began to collect on the surfaces of the reaction vessel. After about five minutes, this spontaneously redissolved and did not reappear. Stirring was continued and the warm solution was allowed to cool for 1.5 hr. At this time a seed crystal, obtained from an earlier reaction, was added to the solution and the mixture stirred at room temperature.

After 8 hr the reaction vessel contained a large amount of solid. This was collected by suction filtration and the mother liquor set aside. The crude product was dried to constant weight, giving a pale yellow solid, 173.9 g (0.86 mol, 37.5%); mp 206° sintering, 214-219° dec.

The deep red mother liquor was heated briefly to reflux temperature and more solid began to precipitate from solution. The mixture was allowed to stand for one day, and the solid was collected by filtration, washed, and dried. This pale yellow solid, 102.4 g (0.51 mol, 22%), gave mp 196-212° dec.

In a similar manner, two additional crops of product were obtained: Crop III: 45.1 g (0.22 mol, 9.7%); mp 198-215° dec; Crop IV: 27.0 g (0.13 mol, 5.8%); mp 222-224° dec. The mother liquor was treated with water to obtain 15b (vide infra).

Crops I and II were combined, dissolved in ethanol
(5.5 l), and the yellow solution filtered. To this was added benzene (1.0 l), and the volume reduced by heating. Although solid began to appear when the volume reached about 4 l, the volume was reduced to 2 l before cooling was allowed. After standing for 8 hr, the solid was collected by suction filtration, washed with copious amounts of alcohol, and dried. This gave a nearly white crystalline solid, 15a, 189 g; mp 223.5-226.0° dec, lit.15 mp 224-226°.

The volume of the mother liquor was reduced to 700 ml and a second crop, 38.4 g, was obtained which exhibited an identical melting point. (After prolonged standing in a sealed container, this substance gives a very pleasant odor when the bottle is opened.)

A sample prepared for analysis by repeated recrystallization from alcohol-benzene gave mp 224-226° dec; uv (c 7.98x10⁻⁵, ethanol) [nm(ε)] 289.6 (13000), 236 (4370), 228 (4900), (Fig. 6).


Infrared Spectrum: Fig. 1; Nmr: Fig. 2.

Picrate. The picrate was prepared in alcohol. The red sticky mass, which initially formed, solidified upon heating the solvent to boiling. The glassy solid thus prepared gave mp 160-170° dec. The solid was digested with boiling alcohol for 0.5 hr and yielded a yellow solid, mp 169.5-171.0° dec. After an extremely difficult recrystallization from alcohol-water, the substance melted at 170.5-
Mol. calc. for \( \text{C}_9\text{H}_{18}\text{N}_4\text{O}_8 \): C, 53.02; H, 4.22.


**Molecular Weight Determination.** The molecular weight was determined via the UV absorption of the picrate anion, after the method of Cunningham, Dawson, and Spring.\(^{57}\) Calcld: 201. Found: 180, 170.

**Semicarbazone, 2,4-Dinitrophenylhydrazone.** Attempts to prepare these derivatives were unsuccessful.

**Oxime.** The oxime was prepared by dissolving 0.5 g of the free base in alcohol containing hydroxylamine·HCl and excess NaOH. The solution was heated for 2 hr, and the oxime was forced from solution by careful addition of acetic acid. The substance, 0.25 g, which was soluble in dilute acid and concentrated base, was collected by suction filtration, washed with water, and dried, giving mp 128-134°.

The tan solid, recrystallized twice from ethanol-water, mp 130-134°, was probably a mixture of syn and anti isomers. Infrared (mull) 1590 cm\(^{-1}\) (C=N=OH).

**Hydrochloride.** The hydrochloride was prepared in tetrahydrofuran yielding a deliquescent white solid which was purified by repeated dissolution in ethanol followed by rapid addition of ether. Drying the sticky solid at 120° overnight gave a pale yellow solid, mp 239.0-241.0° dec; lit.\(^{15}\) 240-241° dec.
Enol Acetate 19. A typical preparation of the enol acetate is described. To a solution of acetic anhydride (35 ml, 0.37 mol) in pyridine was added 15a (45.0 g, 0.224 mol). The solution, which gradually turned red, was heated to reflux temperature for 2.5 hr, allowed to cool, and poured into ice water with stirring. Dilute base was added to bring the pH to 8-10, and an orange oil precipitated. The liquid was decanted, and cold water added causing partial solidification. The semisolid was dissolved in THF, the solution treated with Norite, dried ($\text{MgSO}_4$), and filtered. The pale orange solution was heated to boiling and hot ligroin (bp 90-115°) added until precipitation commenced. The yellow solid thus obtained was collected by filtration, washed with cold ether and dried, yielding 23.0 g (40%) of the enol acetate (19); mp 169.5-172.0°. Additional product, 10.3 g (18%), was obtained upon concentration of the filtrate.

The first crop, recrystallized twice from ligroin, and dried at 100° at 0.1 mm gave mp 178.5-180.5°; uv (C 4.72x10⁻⁵, ethanol) [nm (ε)] 286.4 (15600), 235 sh (4400), 227 sh (5400); ir, Fig. 4; nmr, Fig. 5.

Anal. Calcd for C₁₅H₁₇NO₂: C, 74.04; H, 7.06.
Found: C, 74.11; H, 7.24.

Hydrolysis of Enol Acetate 19. Enol acetate (19) (1.2 g, 0.012 mol) was dissolved in methanol, and 10 g of sodium hydroxide was added to this solution. After standing at ambient temperature for 3.0 hr, the solution was poured into cold water and the white solid which formed was collected
by filtration, washed with water, and dried, yielding 0.85 g (86%) of 15a; mp 216.0-219.5° dec. A mixture melting point determination with an authentic sample of 15a gave mp 217.0-223.0° dec. The infrared and nmr spectra were identical.

1-Methyl-3-benzal-4-piperidone Isomer b (15b). Addition of water to the reaction mixture from which 15a had been isolated resulted in the immediate formation of impure isomer b. The bright yellow solid was collected by filtration, washed with ethanol-water, and dried, giving 76.4 g (16.5%); mp 91-97.5°.

Crude 15b was dissolved in CHCl₃ and the dark brown solution was washed with water, treated with Norite, dried (MgSO₄), and filtered. The resulting red solution was extracted with 3 portions of dilute HCl. The aqueous fractions were combined, and then extracted with small amounts of CHCl₃ until no more color passed into the organic layer. The light orange aqueous solution was extracted once with 100 ml ether and then heated to drive the organic solvent from solution. The solution was cooled by addition of ice and made basic with dilute K₂CO₃. A yellow solid precipitated immediately. This was collected by filtration, washed with water, and the cake sucked as dry as possible. A small portion, dried separately, melted at 113.0-121.0° dec.

The remainder of the substance was dissolved in ethyl acetate and the water layer decanted. Washing the organic layer with saturated sodium chloride caused a yellow semisolid to precipitate from solution. This was collected,
washed with ethyl acetate, and dried, giving nearly colorless \(15a\), mp 219.0-225.0\(^\circ\) dec.

Isomer \(b\) was obtained on addition of ligroin (bp 90-115\(^\circ\)) to the hot ethyl acetate solution, followed by slow evaporation. Several crops of yellow crystalline material were obtained (73.8 g), the purest of which gave mp 124.0-126.5\(^\circ\). This sample, after recrystallization from ligroin (90-115\(^\circ\)), gave no change in mp; uv (c 3.03x10^-5, ethanol) [\(\text{nm (}\epsilon\text{)}\)] 347 (366), 287.0 (7750), (Fig. 6); ir (mull) 4000-3100 clear (no OH), 1720 (C=O), 765, 695 cm^-1 (monosub, phenyl); nmr (CDCl\(_3\)) 2.17 singlet (N-CH\(_3\)), 7.23 broad singlet (phenyl) ppm. The remainder of the protons appeared as a series of broad unresolved bands between 1.8 and 4.0 ppm.

A mixture melting point determination with \(15a\) gave partial melting near 125\(^\circ\) with loss of the yellow color, resolidification at 160\(^\circ\), and complete melting at 208-214\(^\circ\) dec. This appeared to indicate that \(15b\) was isomerizing to \(15a\) upon heating.

**Conversion of \(15b\) to \(15a\)**. Isomer \(b\) (10.9 g) was dissolved in 100 ml ether and the yellow solution heated under reflux for 12 hr. The solution was cooled and the white solid collected by filtration, 1.6 g; mp 221.0-223.0\(^\circ\) dec. A mixture melting point with \(15a\) gave mp 222.0-225.0\(^\circ\) dec.

**Conversion of \(15a\) to \(15b\) via Ultraviolet Isomerization**. A sample of \(15a\) (ca. 1 g) was dissolved in CHCl\(_3\) and the solution irradiated with a Black-Ray (UVL 22) for 2 hr during
which time the solution changed from a pale yellow to a brilliant yellow. Removal of the solvent under reduced pressure gave a bright yellow solid which exhibited behavior identical to that of a mixture of 15a and 15b when heated in a melting point capillary; partial melting was followed by color loss and resolidification. The melting point of the resolidified mass was 220.0-223.0° dec.

**Thin Layer Chromatography Data.** A tlc plate coated with alumina was spotted with pure 15a, pure 15b, and a mixture of the two. After development with CHCl₃, examination under ultraviolet light showed one spot for 15a, R_f 0.22; 15b R_f 0.47 and ca. 0.2, very faint; mixture, R_f 0.25 and 0.47. A second plate was spotted with isomerized 15a from above and after development with CHCl₃, two spots could be seen: R_f 0.25 and 0.44.

A third plate, developed with ethyl acetate, gave for 15a one spot at the origin, R_f 0.00; 15b, one spot, R_f 0.64; isomerized 15b, R_f 0.00 and 0.65. Iodine vapor development showed the presence of no other components.

**Hydrochloride.** The hydrochloride of 15b was prepared by passing HCl through an ethereal solution of the free base. A yellow solid was collected by filtration, washed, and dried; mp 235-238° dec. An analytical sample was obtained by dissolving the substance in ethanol followed by precipitation with ether; mp 234.0-236.0° dec; uv (c 2.1x10⁻⁴, alcohol) [nm (€)] 346.0 (834), 286.8 (9300).

**Anal.** Calcd for C₁₃H₁₆NOC1: C, 65.67; H, 6.80;
N, 5.89 and calcd for C_{13}H_{16}NOCl\cdot\frac{1}{3}H_2O: C, 64.06; H, 6.90; N, 5.75. Found: C, 64.29; H, 6.89; N, 5.89.

After prolonged redrying of the sample (100° at 0.1 mm), it gave mp 225.0-227.5° dec.

Anal. Found: C, 65.63; H, 6.88; N, 5.83.

**Enol Acetate of 15b.** To a solution of 15b (20.2 g, 0.20 mol) in 125 ml pyridine was added acetic anhydride (32.3 g, 0.32 mol). The red solution was heated to reflux for 0.5 hr and allowed to cool for 2.5 hr. The solution was again heated briefly to reflux temperature, allowed to cool, and poured into ice water. The solution was made basic with dilute sodium hydroxide to pH 8-9, and the tan oily solid which formed was separated by decantation. This was dissolved in chloroform and the solution washed with water until no more color passed into it and the odor of pyridine could no longer be detected. The chloroform solution was dried (MgSO_4), treated with Norite and filtered. To this solution was added 100 ml ligroin (95-115°) and the solution slowly deposited 16.3 g (67%) of solid which was a mixture of both enol acetates 19a and 19b. After repeated recrystallization of the low melting fraction from ether-ligroin, a yellow substance was obtained which may have been the enol acetate of 15b; mp 105.2-107.0°; uv (ε 8.35x10^{-5}, ethanol) \([nm (ε)] 448.8 (35), 347 (660), 287.5 (10450); ir (mull) 1755 (CO), 755, 675 (C_6H_5) \text{cm}^{-1}\). This substance decomposed on standing and could not be analyzed.
**Attempted Reduction of 15a to 16**

**Catalytic Reduction of 15a.** In a typical reaction, 15a (25.0 g, 0.124 mol) was dissolved in 100 ml dilute HCl, platinum oxide (0.5 g) added and the mixture subjected to hydrogenation on the Burgess-Paar apparatus at 30 psig. After the uptake of hydrogen ceased, the colloidal platinum was removed with the aid of a fritted glass funnel with gravity flow. To the filtrate was added Na₂CO₃ to pH 9 and a white solid precipitated which was collected via filtration, washed with water and dried, giving 25.0 g (99%); mp 95.5-101.5°.

The infrared spectrum showed bands at 3600 (OH) and 1700 cm⁻¹ (C=O). The product appeared to be a mixture of the alcohol 16 and the ketone 26. This was substantiated by the presence of a carbonyl band at 283 nm (ε 120) in the ultraviolet spectrum.

A longer reaction time failed to yield a product in which the carbonyl group was completely reduced. Separation was not achieved by chromatographic procedures.

**1-Methyl-3-benzyl-4-piperidinol (16).** A solution of the mixture above (30.0 g, ca. 0.15 mol) in THF was added to a slurry of LiAlH₄ (10 g, xs) in THF. The mixture was heated to reflux temperature for 8 hr, and excess hydride decomposed by addition of alcohol, followed by water. The white solid was separated by filtration, washed with THF and the washings were added to the filtrate. The pale yellow solution was buffered to pH 6 and allowed to stand for 12 hr;
a small amount of solid which had formed was removed from
the solution by filtration. To the clear yellow solution was
added 600 ml water followed by saturated Na₂CO₃ to pH 8. A
white solid was collected by filtration, washed to remove all
traces of base, and dried at 60° (20 mm). After 48 hr, con­
stant weight was reached, giving 29.5 g of white solid; mp
106.5-109.0°; ir (CCl₄) 3600, 3500-3100 (OH), 1600-1800 clear
(no CO) cm⁻¹. This substance was soluble in most organic
solvents and dilute HCl. Recrystallization gave only oils
except with paraffin solvents such as pentane or hexane.
In these cases a crystalline solid was obtained albeit of
large mp ranges (e.g. mp 98-117°). This probably resulted
from occlusion of solvent (vide infra). Elution chromato­
graphy failed to separate the isomers or improve the melting
point range.

Hydrobromide. The hydrobromide, prepared from ether­
eal solution, was isolated as an extremely hygroscopic white
solid. After extensive drying, it melted at 184.0-215.0°.
Due to its hygroscopic nature it was not worked with further.

Hydrochloride. The hydrochloride was also prepared
but failed to give satisfactory recrystallization. The salt,
after repeated precipitation from alcohol with ether, exhi­
bited mp 188.5-198.0° dec; uv (ε 7.5x10⁻³, ethanol) [nm (ε)]
340 (9.6), 267.1 (99), 263.8 (143), 260.6 sh (143), 258.0
(179), 252.5 (144), 247.6 (106), 242.3 (74), 237 sh (45),
217 sh (3500), 209.5 (6100), 205.5 (6480).

Picrate. The picrate, obtained from ethanol as a
yellow crystalline solid, melted over a hundred degree range, indicating occlusion of solvent. After drying for 3 hr at 50° (4 mm), it melted at 136-149° dec. Attempted recrystallization from several solvents gave, in all cases, dark semi-solid oils.

**Esterification with Acetyl Chloride.** The diastereomeric alcohol mixture (7.4 g, 0.03 mol) was dissolved in acetyl chloride (25 ml) and the solution heated at gentle reflux for 3 hr. Water was added, and the solution was extracted with 3 portions ether. The aqueous layer was made basic with dilute K₂CO₃ and the product extracted into two 100-ml portions ether. Washing, first with two portions of water and then with saturated NaCl solution, was followed by Norite treatment and drying (MgSO₄). The solvent was evaporated from the resulting clear yellow solution, under reduced pressure, yielding a yellow oil.

The oil was dissolved in dilute HCl, and the solution was made basic with dilute K₂CO₃. A light tan solid (7.9 g) was obtained, mp 57-78°, which gave a strong band at 1740 cm⁻¹ (CO) in the ir spectrum. Elution chromatography failed to resolve the mixture.

**Reduction of Enol Acetate 19 over Platinum Oxide.** Enol acetate 19 (13 g, 0.053 mol) was dissolved in ethanol-water (1:1) and acidified to pH 4 with dilute HCl. The substance was submitted to hydrogenation on the Burgess-Paar apparatus (35 psig) for 2.75 hr in the presence of platinum oxide. When the uptake of hydrogen ceased, the catalyst was
removed by filtration and the solution diluted with water. Slow addition of $K_2CO_3$ to pH 8-10 resulted in the precipitation of a white solid which was collected by filtration and washed with water. Purification by acid treatment and re-precipitation from basic medium yielded 9.49 g (73%) of crude product; mp 84.0-93.0°; ir (mull) 1750 cm\(^{-1}\) (CO).

Column chromatography over alumina (4.0 cm x 31 cm) using isopropyl alcohol as the eluent gave 1-methyl-3-benzyl-4-piperidinol acetate (27), 7.06 g; mp 57-80°. This melted at 93.0-95.0° after recrystallization from isopropanol-water, and was used without further purification in the next step.

Reduction of 1-Methyl-3-benzyl-4-piperidinol Acetate (27) with LiAlH\(_4\). The acetate ester 27 (5.7 g, 0.023 mol) was reduced with LiAlH\(_4\) in 100 ml ether. The mixture was heated briefly to reflux temperature and allowed to cool. After the excess hydride had been destroyed with alcohol followed by water, the mixed hydroxides were separated via filtration. The ethereal solution was washed with water and dried with NaCl solution. Drying was completed ($MgSO_4$) and the drying agent separated via filtration. To the filtrate was added 100 ml ligroin, and the solution evaporated until solid just began to form. Cooling yielded a white crystalline solid, 4.7 g (100%); mp 114.5-119.0° soften, ca. 135° melt; ir (mull) 3350-3100 m, broad (OH) cm\(^{-1}\) (Fig. 7); uv (c 1.44x10^{-2}, ethanol) [nm (ε)] 335.5 (11), 306 sh (16), 285 sh (24), 268.1 (150), 164.0 (186), 261.0 (211), 258.3 (237), 252.7 (224), 247.5 (207), 241.7 sh (212), 217.5 inf
(5040), 209.4 (8700), 206.0 (8750); nmr (CDCl₃) 7.23 singlet (phenyl), 2.05 singlet (N-CH₃) ppm. The remainder of the spectrum appeared as series of broad peaks which could not be identified, although it appeared that signals between 0.0 and 2.0 ppm resulted from hydrocarbon impurities. On drying at reduced pressure no differences in the properties of the substance were detectable, but if heating were applied to enhance drying the substance seemed to decompose, and even wider melting point ranges were observed. Samples submitted for analysis consistently gave high values for carbon, e.g.: Anal. Calcd for C₁₃H₁₉NO₂: C, 76.04; H, 9.35; N, 6.82. Found: C, 77.71; H, 9.15; N, 6.38. Other analyses gave C, 77.0-78.1. This probably reflects the ability of this substance to trap or "include" paraffin solvents. The frothing observed during drying at 100° probably resulted from loss of these solvents and not from decomposition of product.

1-Methyl-3-benzal-4-piperidinol (28). Compound 15a (4.5 g, 0.02 mol) was suspended in 100 ml THF and LiAlH₄ was added to this mixture. Sufficient heat was generated to bring the solvent to reflux temperature, and the mixture was allowed to stand for 1 hr. The work-up was similar to that described for 16 above, yielding a pale yellow crystalline solid, 4.0 g; mp 67-119°. A small sample, dried at 80° for 15 min, gave mp 73.0-118.5°; nmr (CDCl₃) 7.23 singlet (C₆H₅), 6.87 singlet (vinyl), 2.04 singlet (N-CH₃) ppm. Numerous peaks between 0.5 and 1.8 ppm again indicated occluded solvent. A well-
ground sample dried at 80° for 12 hr gave an identical mp value and nmr spectrum.

Approximately 250 mg of product was placed in an evaporating dish and the substance heated until the entire mass was fused. This temperature was maintained for several minutes and the melt was constantly stirred. As the substance cooled, a yellow glass formed. This was ground, giving a yellow powder, mp 122.0-124.5°. The nmr spectrum showed no solvent peaks but was otherwise unchanged, indicating that the occluded solvent had been lost on heating and that decomposition had not occurred. The uv spectrum showed only one band at 240 nm (ε 7500) consistent with the styryl chromophore of 28.

Attempted PPA Cyclization of 1-Methyl-3-benzyl-4-piperidinol (16). The crude alcohol 16 (10.8 g, 0.05 mol) was dissolved in 100 ml polyphosphoric acid. The viscous, stirred solution was heated to 150-160° for 45 min and the hot solution poured into ice water and neutralized with NaOH. A tan product precipitated and was collected by filtration, giving 7.5 g of tan solid; mp 59.5-60.0°; ir (mull) 762 vs, 704 vs (monosub. phenyl) cm⁻¹; ir (CCl₄) 1952, 1880, 1815, 1755 vw (monosub. phenyl) cm⁻¹, 58

Nmr (CDCl₃) 7.25 singlet (phenyl), 3.95 broad singlet (possibly vinyl), 2.24 singlet (N-CH₃) ppm. The remainder of the spectrum could not be interpreted. Apparently only dehydration had occurred.

The hydrochloride, a pink solid, was prepared in
ether, mp 211-216° dec.

Attempted Cyclization with $P_4O_{10}$. 1-Methyl-3-benzyl-4-piperidinol (16) (5.00 g, 0.024 mol) was mixed with $P_4O_{10}$ (6.9 g, 0.024 mol) in a vented flask and heated with the aid of an oil bath to 145° for 0.5 hr. A semisolid mass formed. To this was slowly added 100 ml ice-water and the mixture carefully stirred in order to dissolve all oils. The solution was extracted twice with ether and made basic with $Na_2CO_3$. A tan solid was collected by filtration, washed with water, and purified by extraction into acid and reprecipitation with $Na_2CO_3$. The resulting white solid, 3.95 g, had spectra similar to those of the product obtained by PPA conditions, indicating that simple dehydration had again occurred.

Attempted Cyclization of 16 with $P_4O_{10}$ in Refluxing Bromobenzene. The alcohol 16 (3.0 g, 0.015 mol) was dissolved in bromobenzene and $P_4O_{10}$ (6 g) was added. The mixture was heated to reflux temperature for 45 min and poured into ice water. Work-up yielded an olefinic substance, 1.0 g; mp 83-85°; ir (mull) 1680 (olefin), 755, 700 (monosub. benzene) cm$^{-1}$. This substance was not worked with further.

Preparations of 8-Tetralone (30) and 6-Methoxy-2-tetralone (35)

Preparation of Phenylacetyl Chloride. A mixture of phenylacetic acid (140 g, 1.0 mol) and thionyl chloride (135 g, 1.1 mol) was heated to reflux temperature for 0.5 hr. The resulting dark liquid was distilled under reduced pressure to give a nearly colorless liquid, bp 70-75° (0.2-0.5 mm);
Preparation of β-Tetralone (30) via the Friedel-Crafts Reaction. In the best of seven reactions, phenylacetyl chloride (37.2 g, 0.24 mol) was added dropwise, over a period of 2 hr, to 1.2 l carbon disulfide, which was cooled in an ice bath and contained AlCl₃ (64 g, 0.48 mol). Throughout the course of the reaction, dry ethylene gas was bubbled through the solution and the reaction mixture stirred. Following the addition of the acid chloride, 3 g of fresh AlCl₃ was added. The ethylene flow was interrupted after 4 hr and the reaction mixture poured into a mixture of ice and concd HCl. This mixture was well stirred to dissolve the large amount of polymeric materials present; the two layers were separated and the aqueous layer extracted twice with 100 ml CS₂. The washings were added to the CS₂ layer, and this, in turn, washed three times with 250 ml water. The reddish solution was dried (MgSO₄), and the solvent removed under reduced pressure. A dark red oil remained which gave a positive β-tetralone blue test. This was dissolved in 50 ml ether and extracted, in turn, with 100 ml water, twice with dilute Na₂CO₃, twice with water, and finally with cold saturated NaCl solution. The solvent was removed under reduced pressure and the resulting oil distilled. The fraction distilling at 185-195° (120-140 mm) was collected, (lit.²⁸ 114-116° at 4.5 mm); 23.5 g (67%); ir (film) 1725 vs (CO), 750 (ortho-disub. phenyl) cm⁻¹.
2-Naphthyl Ethyl Ether. 2-Naphthol (170 g, 1.18 mol) and anhydrous potassium carbonate (166 g, 1.20 mol) were dissolved in 150 ml water, with cooling. To this stirred solution was added ethyl iodide (197 g, 1.26 mol) in 100 ml acetone. The solution was heated under reflux for 2 hr, at which time a test for the phenol showed that reaction was complete.

The reaction mixture was cooled and the aqueous layer decanted from a heavy oil and extracted with two 100-ml portions of benzene. The extracts and oil were combined and extracted twice with K₂CO₃ solution and then with three portions of saturated NaCl. After purification with Norite, the dried (K₂CO₃) benzene solution was concentrated to yield a red oil which tended to solidify upon cooling, mp 25-50°.

To the solid was added 500 ml of 2 N NaOH and the mixture heated. The basic solution turned yellow and an oil formed on the surface. Heating was continued for 0.5 hr with stirring, and the mixture was cooled in an ice bath. The solidified oil was collected by filtration, and the lumps were crushed and thoroughly washed with water. After drying, the product (89 g, 44%) melted at 34-36°. Recrystallization from ethanol-water gave 69.5 g of 2-naphthyl ethyl ether, mp 34.8-36° (lit. 35.5-36.0°); nmr (CDCl₃) 0.90 triplet (3H), 3.35 quartet (2H), 7.0 multiplet (7H) ppm.

β-Tetralone (39) from 2-Naphthyl Ethyl Ether via the Birch Reduction. β-Tetralone was prepared according to the method of Soffer, Bellis, Gellerson, and Stewart. The product was isolated as the sodium bisulfite adduct in yields
of 53-57%. The nmr spectrum (D₂O) of the adduct showed 2.15 and 2.83 \( A_2B_2 \) (4H), 3.10 singlet (1H), 3.22 singlet (1H), 7.11 singlet (4H, aromatic), 4.6 singlet (D₂O) ppm.

A small amount of the pleasant smelling ketone was regenerated. Removal of solvent, diethyl ether, under reduced pressure, gave \( \beta \)-tetralone, nmr (neat) 2.25 and 2.86 \( A_2B_2 \) (4H), 3.35 singlet (2H), 7.05 poorly defined triplet (4H) ppm. Small peaks at 1.08 triplet and ca. 3.35 quartet ppm were assigned to diethyl ether. Since small amounts of starting material or ether would not interfere in the next step, \( \beta \)-tetralone was used without further purification.

**p-Methoxyphenylacetyl Chloride.** p-Methoxyphenylacetic acid (51 g, 0.31 mol) was mixed with thionyl chloride (21.5 ml, 0.30 mol) and the mixture brought to gentle reflux for 1 hr. The condenser was removed and the liquid heated briefly to 90° in order to drive out remaining SOC\(_2\)Cl; the light orange oil was distilled under reduced pressure. After discarding a small fore-run, the fraction distilling at 118.0-119.0° (4.5 mm) was collected; 54 g (96%); ir (smear) 1795 (RCOC\(_1\)) cm\(^{-1}\); nmr (neat) 3.33 singlet (3H), 3.64 singlet (2H), 6.65 AB quartet (4H) ppm. This was used directly in the next step.

**6-Methoxy-2-tetralone (35).** In a 3-necked, round-bottomed flask, fitted with a delivery tube for ethylene gas, a dropping funnel, and a stirrer, was placed 400 ml CS\(_2\). This was cooled in an ice bath and maintained at 0° for the duration of the reaction. The ethylene was adjusted
to bubble slowly through the stirred solvent, and over a period of 1.25 hr, \( p \)-methoxyphenylacetyl chloride (50 g, 0.27 mol) and, in small portions, \( \text{AlCl}_3 \) (70 g, 0.53 mol) were added. The ethylene flow was continued for 15 min after addition of the reagents. The solvent was decanted and water added to the gummy mixture with stirring. The \( \text{CS}_2 \) was evaporated in a water bath in the hood, and water was added to the remaining oil. Both portions were extracted with ether, and the extracts were combined, treated with Norite, dried (\( \text{MgSO}_4 \)), and the solvent removed under reduced pressure. This left a dark oil which gave a positive \( \beta \)-tetralone blue test.

**Formation of the Bisulfite Adduct.** To the oil obtained above was added 50 ml saturated \( \text{NaHSO}_3 \). Shaking produced noticeable cooling, but no solid formation. Cooling the solution in dry ice-acetone gave a tan solid, which was collected by filtration, washed with cold ethanol and ether. The solid was transferred to a beaker and washed again with cold ethanol. The pale yellow solid was collected by filtration, washed with ether, and dried, yielding 9.3 g (13%) of 6-methoxy-2-tetralone sodium bisulfite adduct.

A small amount of the light yellow ketone (35) was regenerated; ir (smear) 2820 (OCH\(_3\)), 1720 (CO), 880, 820 (1,2,4-trisub. phenyl) cm\(^{-1}\). Due to the small amount of product obtained, it was used without purification for the Mannich reaction.
The Mannich Reaction

3-Methyl-6,7-benzo-3-azabicyclo[3.3.1]nonene-9-one (31).

Procedure A. This reaction was modeled on the method of House, Wickham and Muller but was unsatisfactory in its failure to yield a product of satisfactory purity. In a typical reaction, 8-tetralone (4.92 g, 0.034 mol), methylamine hydrochloride (2.03 g, 0.037 mol), and 40% formaldehyde (7.4 ml, 0.23 mol) were dissolved in 67 ml glacial acetic acid. The resulting yellow solution was heated on a steam bath for 3.5 hr.

Water (100 ml) was added, the solution neutralized with dilute NaOH, and the aqueous layer extracted with 3 portions of CHCl₃. The extracts were combined and the product was extracted into three 150-ml portions of dilute HCl. A brown tar, insoluble in dilute HCl, CHCl₃, and acetone, remained in the separatory funnel and was discarded. The aqueous extracts were combined and neutralized with K₂CO₃ to pH 9 and extracted with CHCl₃. The solvent was removed under reduced pressure giving a dense brown oil, 4.18 g, which tended to solidify under cyclohexane. Thin layer chromatography data (alumina) indicated that this semisolid was a mixture of at least two components. No satisfactory method, including chromatography, could be devised by which either component could be purified. It did appear that a trend toward a high melting product, mp 180-200°, and a lower melting substance, mp 129.5-133.0°, could be seen.

The hygroscopic hydrobromide was prepared, mp 117-130° soften, 160-162° dec, which also could not be purified.
The picrate was formed, mp 172-178° dec. A molecular weight determination using the method of Cunningham, Dawson, and Spring gave ca. 150 for the free base, and therefore indicated that the product was \( 31 \) (MW 201.3) rather than \( 33 \) (MW 347.5).

**Procedure B. Drop-in Technique.** In a generalized procedure, methyl amine hydrochloride (6.95 g, 0.104 mol) and 40% aqueous formaldehyde (25 ml, 0.3 mol) were dissolved in 1 l acetic acid. The solution was heated to 100°, with continuous stirring throughout the course of the reaction. To this, over a period of 3.0 hr, was added dropwise a solution of \( \beta \)-tetralone (15.0 g, 0.103 mol) in 50 ml acetic acid. The reaction flask was protected from direct exposure to light throughout the course of the reaction. After all of the ketone had been added, an aliquot was removed and subjected to the \( \beta \)-tetralone blue test. A negative test indicated completion of the reaction.

The reaction flask was removed from heat and the solvent removed under reduced pressure with gentle steam heating, requiring about 1.5 hr. To the light orange oil was added 500 ml water and 5 ml concd HCl. The oil remained dispersed in the water layer and could not be separated. The mixture was extracted with 100-ml portions of CHCl₃ until no more color passed into it. This left a pale yellow aqueous solution. The first chloroform extract was extracted once with 200 ml water and this, in turn, by two 100-ml portions of CHCl₃. This pale yellow, slightly acidic solution
was added to the acid layer above. The solution was filtered and the dissolved chloroform driven out with gentle heating under aspirator pressure.

The clear yellow solution was transferred to a large beaker, ice added, and with constant stirring the solution was taken to pH 9-10 with $K_2CO_3$ solution. A light tan solid began to form slowly. This mixture was allowed to cool in the refrigerator for several hours, giving a light tan microcrystalline solid. It was collected by filtration, washed with water, and dried ($K_2CO_3$), yielding 7.87 g (38%); mp 93-96°. (Other reactions gave 11-56% and similar melting point ranges at this stage.)

The crude product was dissolved in ethanol-CHCl₃ (1:1), treated with Norite, filtered, and then eluted through a short column of Florisil (or alumina) with CHCl₃ to remove some of the polymeric material present. The base (5 g) was dissolved in hot methanol; a small amount of insoluble material was separated and discarded. Upon cooling, a light tan solid formed, 300 mg; mp 185-196° dec, which was discarded. Reduction of the volume of the solvent on a hot plate, until solid just began to form, followed by cooling, gave a light tan solid, 1.60 g, which, after drying at 100° (0.02 mm) for 4 hr, gave mp 157.5-159.0° dec. An analytical sample, recrystallized from methanol and dried at 100° (0.1 mm) for 20 hr, melted at 156.5-158.5° dec.

Ir (CHCl₃) Fig. 9; nmr (CDCl₃) Fig. 10; uv (c 3.62x10⁻³, methanol) [nm (ε)] 333.5 (592), 322.7 (532), 290.7 (1215), 279.6 (1470), 272.5 (1560), 230.3 (13300).

This substance tends to decompose slowly upon standing, even in a sealed container; it could not be stored for long periods of time as the free base. The decomposition product is sparingly soluble in most solvents, with the exception of chloroform, and exhibits a mp near 200⁰. It was not characterized.

**Picrate.** The picrate was prepared from ethanol, mp 172.5-173.5⁰; molecular weight, calcd 201.3, found 201.

**Hydrochloride.** The hydrochloride was prepared by passing hydrogen chloride through a solution of the base in ether-THF or THF and melted at 199-204⁰ dec. The salt, purified by dissolution in ethanol followed by precipitation with ether, gave mp 202.0-203.5⁰ dec; nmr (D₂O) 2.45 poorly resolved doublet (N-CH₃), ca. 7.1 broad (phenyl), 4.30 singlet (DOH) ppm. The remainder of the spectrum, a series of broad, non-resolved peaks, could not be interpreted. Inspection of the integration showed, for relative areas, phenyl:non-aromatic: 4:10.5 (calcd 4:11). The area under the DOH peak integrated for 5.1 H. The solvent, using identical settings on the instrument, showed a small spike at 4.5 ppm (0.1 H) indicating that the DOH peak represents not only the HCl proton but also two waters of hydration.

This salt, heated under reduced pressure, tended to give lower decomposition points of increased range. A
minimum value of 186.0-187.5° dec was obtained by heating at 100° (0.02 mm) for 24-36 hr.

**LiAlH₄ Reduction of 31 to 3-Methyl-6,7-benzo-3-aza-bicyclo[3.3.1]nonen-9-ol.** The free amine (31) (2.85 g, 0.014 mol) was dissolved in 100 ml dry THF, treated with 4 g LiAlH₄, and the mixture heated to reflux for 5.5 hr. The excess hydride was decomposed with alcohol and the waxy solid removed via filtration. The filtrate was transferred to a separatory funnel, 100 ml each of water and ether added, and the product extracted into the ether layer. The organic layer was washed with water and dried (MgSO₄). The drying agent was removed by filtration, and the solvent was removed under reduced pressure, yielding 2.8 g (90%) of solid; mp 148.5-151.0° after recrystallization from CH₃OH-H₂O.

This substance exhibited a faint amine-like odor. 

\[ \text{IR (mull) 3300 broad (OH), 1450, 1260, 1055 (2° OH), 755 vs (disub. phenyl) cm}^{-1}. \]

**Tosylate.** To a cooled pyridine solution of the above alcohol (1.78 g, 0.0087 mol) in an ice bath, was added tosyl chloride (1.82 g, 0.0096 mol) over a period of 0.5 hr. After 3.3 hr, the reaction was quenched by pouring it into ice water. The bright yellow solid was collected by filtration, washed with water, and dried, 2.07 g (67%). After drying at 100° (0.1 mm) for 3 hr it melted at 162-172° dec; ir (mull) 3400 w (OH or H₂O), 1350, 1175, and 678 (tosylate) cm⁻¹.

Sodium fusion test gave a positive lead acetate test (sulfur). The substance was used without further purification in the next step.
Attempted Preparation of 3-Methyl-6,7-benzo-3-aza-bicyclo[3.3.1]nonene (17). The crude tosylate (1.92 g, 5.3x10^{-3} mol) was suspended in 100 ml dry THF. To this was added excess LiAlH₄ and the mixture heated to reflux for 1 hr. The excess hydride was destroyed with methanol, followed by water, and the precipitate removed by filtration. The product was extracted into ether and washed with water, followed by saturated NaCl. The pale yellow ether solution was dried (MgSO₄) and the solvent removed under reduced pressure yielding a yellow solid, 0.58 g (58%); the ir (mull) showed no absorption from 3100-4000 cm⁻¹.

Recrystallization from methanol gave a product melting at 158.0-159.5°C; ir (mull) 3020 w (aromatic), 759 (ortho-disub. phenyl) cm⁻¹; uv (c 2.9×10⁻⁴, CH₃OH·HCl) [nm (ε)] 324.3 (263), 316 inf (271), 290 inf (950), 273.9 (1385), 267 (1400), 228.5 (4600), 216 inf (ca. 4000). The inflection at 290 nm is probably due to unreacted ketone (31). This sample gave a meaningless elemental analysis; the quantity of the remaining sample was too minute to purify further.

Attempted Preparation of 2′-Methoxy-3-methyl-6,7-benzo-3-azabicyclo[3.3.1]nonen-9-one (34). The bisulfite adduct above (9.3 g, 0.03 mol) was treated with aqueous K₂CO₃ and the free ketone 35 dissolved in ether. Acetic acid (50 ml) was added and the ether removed under reduced pressure. This solution was added dropwise over a period of 1.5 hr to a solution of methylamine hydrochloride (2.48 g,
0.037 mol) and 40% formaldehyde (9 ml, 0.10 mol) in 400 ml acetic acid, maintaining the temperature at 95-105°.

Following a work-up procedure similar to that described for 31, there was obtained 2.1 g of a light yellow solid, mp 142-152°. The infrared spectrum (mull) showed no bands for either the phenyl or carbonyl groups, and the nmr (CDCl₃) failed to exhibit signals for the aromatic protons. The substance was not further characterized.

Resolution of 3-Methyl-6,7-benzo-3-azabicyclo[3,3,1]-nonen-9-one (31)

(+)-Camphor-10-sulfonic Acid as Resolving Agent.
Racemic 31 (2.16 g, 0.011 mol) was dissolved in ether containing a little THF; a small amount of insoluble material was removed by filtration. To this was added a saturated solution of (+)-camphor-10-sulfonic acid until no more precipitate formed. The tan solid was collected by filtration, washed with ether, and dried, giving 2.47 g (54%) of salt melting at 176-178° dec; nmr (CDCl₃) ca. 7.75 broad singlet (4.0 H, phenyl), 0.79 and 1.05 singlets (6.0 H, gem-dimethyl) ppm. The remainder of the spectrum, appearing as a series of broad peaks between 1.2-5.0 ppm, could not be interpreted. The total integration was more revealing; calcd for C₂₅H₃₁NO₅S: ratio of aromatic:non-aromatic protons, 4:27. Found: 4:28. Via an acid-base work-up, ca. 1 g of free base 31 was recovered from the mother liquor.

No solvent could be found from which this substance could be recrystallized; dark oils, or semisolid oils, were
obtained in all cases. In some instances, small differences in the specific rotations could be observed, but in only one case could observable rotations (<0.1°) be measured in a sample of the free base.

Resolution Via (++)-Tartaric Acid. Racemic 31 (4.29 g, 0.021 mol) was dissolved in acetone and a saturated solution of (++)-tartaric acid in acetone was added dropwise until no more solid formed. The product was collected by filtration, washed with acetone, and dried, yielding 2.0 g of salt; mp 137-143°. Upon standing, the mother liquor gave another crop of solid, 0.9 g, melting at 127-143°. Reduction of the volume of the mother liquor gave a third crop of salt, 1.0 g, melting at 116-150°. Addition of ether to the mother liquor gave a fourth crop of solid, 2.3 g, exhibiting mp 90-104°; combined yield 6.2 g (86%).

The specific rotations of these were determined in a 1 dm cell at 26°.

Crop I. (c 2.25, H2O). [α]578 +9.3°, [α]546 +8.4°,

Crop II. (c 3.9, H2O). [α]578 +6.4°, [α]546 +8.4°,

Crop III. (c 1.86, H2O). [α]578 +16°, [α]546 +27°,

Crop IV. (c 1.24, H2O). [α]578 +16°, [α]546 +12°,

(++)-tartaric acid. (c 2.26, H2O). [α]578 +22°,
Purification of Crop III. The salt, 1.0 g, was leached with boiling acetone and the yellow solution decanted from the remaining solid. This was repeated five times, leaving 300 mg of racemic salt. The six acetone solutions were combined, allowed to cool, and the small amount of racemic material which crystallized from solution was removed by filtration. After reduction of the volume the solution deposited 110 mg of (+)-31 tartrate; mp 146.5-148.0°; rotations (c 0.85, H₂O, 26°): [α]₅₇₈ +31°, [α]₄₃₀ +32°, [α]₄₀₅ +57°, [α]₃₆₅ +68°, [α]₃₆₅ +81°.

Regeneration of (+)-31. The free base, (+)-31, was regenerated by dissolving the salt in 2.0 ml H₂O and adding saturated Na₂CO₃ until pH 10 was attained. The resulting tan solid was transferred to a centrifuge tube and after centrifugation, the liquid was decanted and the solid washed with water. The mixture was re-centrifuged and the process repeated until the wash water gave no reaction to test paper. The solid was dissolved in CHCl₃, washed with water, and the amber solution dried (K₂CO₃). Filtration through a pad of glass wool gave a clear orange solution, which, after evaporation of the solvent, left a glassy solid which was crushed, washed with a little ligroin, and dried, giving 59 mg of (+)-31; mp 111-114°; ir (CHCl₃) identical to racemic 31 (Fig. 9); rotations (c 1.05, CH₃OH·HCl) [α]₅₇₈ +25°, [α]₄₃₆ +23°, [α]₄₀₅ +29°, [α]₃₆₅ +38°, [α]₃₆₅ +43°; and (c 0.073, EPA) [α]₅₈₉ +11.7°, [α]₅₇₈ +12°, [α]₄₃₆ +14.5°, [α]₄₀₅ +29°, [α]₃₆₅ +39°, [α]₃₆₅ +66° (Cary 6D).
Purification of Tartrate Salt (Crop I). Crop I above was leached three times with boiling acetone. The remaining solid was dissolved in boiling ethanol, and a small amount of insoluble material was removed by filtration. The clear yellow solution was reduced in volume to 50 ml and hot acetone carefully added until faint cloudiness appeared. Upon cooling, a crop of tan needles (0.55 g), mp 115-117°, was obtained.


The salt was recrystallized once more from ethanol-acetone, giving tan needles (380 mg) melting at 120-125°.

Isolation of (-)-31. The free base, (-)-31, was isolated and regenerated in the same manner as the (+)-isomer, yielding 150 mg (70%); mp 135.0-138.5° dec; ir (CHCl₃) identical with Fig. 9.


_Ultraviolet Spectra._ The uv spectra appeared to be solvent and concentration dependent (Fig. 11):

A. (c 5.43×10⁻⁴, EPA) [nm (ε)] 331.5 (564), 316.8 (593), 290 sh (1170), 278.5 sh (1570), 268 (1640).

B. (c 1.55×10⁻⁴, CH₃OH+HCl (trace)) [nm (ε)] 331 (574), 315.5 (487), 290 (1140), 277 (1160), 267.5 (1500).

(c 7.76×10⁻⁵, CH₃OH+HCl (trace)) [nm (ε)] 290 (1180), 267.5 (1480), 230.5 (12700).

C. (c 1.71×10⁻³, CH₃OH+HCl (trace) + K₂CO₃ (slight xs))
[nm (\(\epsilon\))] 360 sh (278), 330 (567), 317.5 (627).

\((c \, 3.42 \times 10^{-4}, \text{CH}_3\text{OH+HCl+K}_2\text{CO}_3(xs)) [\text{nm (\(\epsilon\))}]

360 inf (146), 330 (298), 217 (324), 292 sh (631), 279 sh (757), 272 sh (818), 265 inf (870), 230 (5040), 203 (ca. 1.5 \times 10^4). The discrepancies here are not due to dilution or calculation errors but seem to reflect some physical or chemical phenomenon; this may be hemiketal or ketal formation.

D. \((c \, 2.63 \times 10^{-3}, \text{H}_2\text{O+HCl (trace)}) [\text{nm (\(\epsilon\))}] 329.5 sh (168), 321 (187), 314 (190), 307 inf (194), 290 sh (369), 275.5 sh (510), 271 sh (540), 266 (560), 225 (5900), 194 (20600). (The last two values were determined at \(c \, 2.3 \times 10^{-5}\).)

**Optical Rotatory Dispersion Spectra.** ORD spectra were determined for both isomers in EPA and acidic methanol. In addition, the spectrum of the (+)-isomer was determined in basic methanol solution; dilutions were made when necessary. Data are reported as nm ([\(\theta\)]).

**Circular Dichroism Spectra.** CD spectra were determined of both isomers in the solutions used above. Data are reported as nm ([\(\theta\)]).

\(\text{(+)-3-Methyl-6,7-benzo-3-azabicyclo[3.3.1]nonen-9-one (\(+\))=31.}

CD \((c \, 3.64 \times 10^{-4}, \text{EPA})\): 335 (0°), 315 sh (+391°), 312 sh (+402°), 304.5 (+572°), 298 (+524°), 294 (+530°), 282.5 (+133°), 281 (0°); \((c \, 7.28 \times 10^{-5})\): 298 (+540°), 281 (0°), 275 (-452°), 260 (0°); \((c \, 1.46 \times 10^{-6})\): 255 (0°), 253 (0°), 240 (+17600°), 235 (+16500°). Fig. 12.
RD (c 1.80x10^-3, EPA): 600 (+21°), 589 (+23.5°), 546 (+29°), 355 (+155°); (c 1.80x10^-4): 375 (+106°), 318 (+525°), 312 inf (+368°), 307.5 inf (+323°), 299.5 (0°), 285 (-480°); (c 3.61x10^-5): 299 (0°), 262 (-720°), 269 (0°), 242.5 (+500°). Fig. 12.

CD (c 3.44x10^-4, CH3OH:HC1): 325 (0°), 320 (+16°), 300 (0°), 295 (0°), 275 (-70°), 260 (-10°); (c 6.88x10^-5): 255 (-187°), 232.5 (-620°), 222.5 (0°), 220 (+200°).

CD (c 3.44x10^-4, CH3OH:HC1 + K2CO3): 327 (0°), 297.5 (+656°), 278 (0°), 270 (-171°); (c 6.88x10^-5): 298 (0°), 275 (-822°), 265 (-986°), 235 (-2070°), 220 (0°). Fig. 13.

RD (c 1.71x10^-4, CH3OH:HC1 + K2CO3): 400 (+77°), 372.5 (+117°), 360 (+87°), 317.5 (+442°), 298.5 (0°), 283 (-605°), 275 (-420°); (c 3.42x10^-5): 330 (+82°), 305 (0°), 282 (-585°), 270 (0°), 252.5 (+374°), 242 (0°), 230 (+1760°). Fig. 14.

CD (c 3.44x10^-5, H2O:HC1): 240 (0°), 222.5 (-1400°), 220 (0°).

CD (c 3.44x10^-5, H2O:HC1 + K2CO3): 272.5 (0°), 250 (-1800°), 247.5 (-1760°), 232.5 (-2820°), 217 (0°), 210 (+1100°).

(−)-3-Methyl-6,7-benzo-3-azabicyclo[3.3.1]nonen-9-one (−)-31.

CD (c 5.46x10^-4, EPA): 332 (0°), 302 (-270°), 299 (-230°), 295 (-260°), 275 (0°), 265 (+120°), 248 (0°).

This spectrum gives only fair agreement with that determined for the (+)-isomer. After all the spectra had
been determined, it became apparent that the instrument had
given erroneous baselines for two separate determinations of
this curve. The data here are corrected as well as possible
on the basis of the other spectra determined for this isomer.

\[
\begin{align*}
\text{RD} & \quad (c \ 1.36 \times 10^{-3}, \ \text{EPA}) \quad 589 (-7^\circ), \ 540 (-13.2^\circ), \\
& \quad 360 (-61^\circ); \quad (c \ 5.43 \times 10^{-5}) \quad 360 (-70^\circ), \ 322.5 (-159^\circ), \\
& \quad 315 \inf (-136^\circ), \ 295 (0^\circ), \ 285 (+129^\circ), \ 270 (0^\circ), \ 267.5 \inf \\
& \quad (-240^\circ), \ 250 (-370^\circ), \ 247.5 (-550^\circ). \\
\end{align*}
\]

Spectral Data of the 6,7-Benzomorphans (7)

Ultraviolet Spectra of the Benzomorphans (7). The
spectra were all obtained in methanol. The initial solutions
\((c \ 3.4 \times 10^{-3} \ \text{to} \ 1.3 \times 10^{-2} \ \text{mol}/1)\) were diluted when necessary.
After the spectra had been determined, the solutions of the
free bases were acidified by addition of one drop of concd
HCl. Solutions of the hydrobromides were made basic by the
addition of one drop of ammonia solution. Hence the spectra
of both the free base and the salt were obtained for all com-
pounds from 300-200 nm. The data are presented below as
nm \((\varepsilon)\).

Optical Rotatory Dispersion Spectra of the Benz-
omorphans (7). The ord spectra were obtained utilizing the
solutions above from 350-210 nm; \((c \ 3.4 \times 10^{-4} \ \text{to} \ 1.3 \times 10^{-3} \ \text{mol/}
100 \ \text{ml})\), diluted when necessary. The spectra of both
the hydrohalide salts and the free bases were obtained.
In addition, the spectra were obtained for the compounds
as supplied on a Rudolph Recording Spectropolarimeter,
denoted \((R)\), from 611 to 240 nm; initial concn 1.1 to
6.7x10^{-4} \text{ mol/100 ml}. The results of both sets of spectra are recorded below as nm ([\phi]).

Circular Dichroism Spectra of the Benzomorphans (7).
The cd spectra were obtained in the region 325-210 nm for both the acid and base forms of these compounds. The solutions utilized for the uv and ord spectra were also used here. The initial concentrations expressed in g/cc were 1,1-3.3(10^{-3}). The data are recorded below as nm ([\theta]).

\(\alpha\)-(−)-2′-Hydroxy-2,5,9-trimethyl-6,7-benzomorphan (7a).

**Free base:**

UV (c 2.53x10^{-4}): 287.5 sh (2150), 281 (2400), 227.5 sh (5780), 220 (6240). Fig. 17.

CD (c 5.84x10^{-5}): 302 (0°), 288.5 (-4080°), 285 (-4000°), 282 (-4440°), 251.5 (0°), 245 (0°), 227 (+5540°), 214 (0°), 210 (-6620°).

RD (c 5.06x10^{-5}): 325 (-1240°), 294 (-4210°), 279 (0°), 268.5 (+1050°), 254 (0°), 243 (-375°), 238 (0°), 227.5 inf (-5450°), 210 (-20000°). Fig. 19.

RD (R) (c 6.73x10^{-4}): 288 (-3410°), 276 (0°), 266 (+1040°), 236 (+220°).

HCl added:

UV (c 2.53x10^{-4}): 288 sh (2030), 281 (2320), 227.5 (6360), 221 (6120). Fig. 17.

CD (c 5.84x10^{-5}): 302 (0°), 289 sh (-4160°), 281 (-4790°), 276 sh (-4160°), 253 (0°), 244,5 (0°), 227.5 (+11100°), 215 (0°), 210 (-2300°).

RD (c 2.54x10^{-5}): 325 (-1580°), 294 (-4680°),
\(278.5 \, (0^\circ), \ 268.5 \, (+1060^\circ), \ 255 \, (0^\circ), \ 247.5 \, (-315^\circ), \ 245 \, (0^\circ), \ 235.5 \, (+2240^\circ), \ 232.5 \, (0^\circ), \ 225 \, (-7250^\circ), \ 215 \, (0^\circ), \ 207.5 \, (-22300^\circ). \) Fig. 19.

\(8\, (-)-2\,'-\text{Hydroxy}-2,5,9\,-\text{trimethyl}-6,7\,-\text{benzomorphan}\cdot\text{HBr} \, (7b).\)

\(\text{UV} \ (\epsilon \ 2.59 \times 10^{-4}): \ 288 \, \text{sh} \, (2000), \ 281 \, (2270), \ 227 \, (6155), \ 220.5 \, (6050).\)

\(\text{CD} \ (\epsilon \ 8.10 \times 10^{-4}): \ 297.5 \, (0^\circ), \ 292 \, \text{sh} \, (-2660^\circ), \ 285 \, (-3740^\circ), \ 261 \, (0^\circ), \ 245 \, (0^\circ), \ 228 \, (+8020^\circ), \ 212 \, (0^\circ), \ 210 \, (-1510^\circ).\)

\(\text{RD} \ (\epsilon \ 1.04 \times 10^{-4}): \ 345 \, (-1150^\circ), \ 293 \, (-3970^\circ), \ 279 \, (0^\circ), \ 270 \, (+990^\circ), \ 250 \, (+1930^\circ), \ 237 \, (+1800^\circ), \ 232 \, (0^\circ), \ 225 \, (-7000^\circ).\)

\(\text{NH}_4\text{OH added;}
\)

\(\text{UV} \ (\epsilon \ 2.59 \times 10^{-4}): \ 288.5 \, \text{sh} \, (2020), \ 282 \, (2250), \ 228 \, \text{sh} \, (5440), \ 220 \, \text{sh} \, (6110).\)

\(\text{CD} \ (\epsilon \ 8.10 \times 10^{-5}): \ 300 \, (0^\circ), \ 290 \, \text{sh} \, (-2980^\circ), \ 284 \, (-3630^\circ), \ 260 \, (0^\circ), \ 233 \, (0^\circ), \ 222 \, (+2940^\circ), \ 215 \, (0^\circ), \ 214 \, \text{sh} \, (-2320^\circ), \ 210 \, (-6100^\circ).\)

\(\text{RD} \ (\epsilon \ 2.59 \times 10^{-5}): \ 325 \, (-1160^\circ), \ 294 \, (-3440^\circ), \ 278 \, (0^\circ), \ 270 \, (+7730^\circ), \ 254 \, (0^\circ), \ 236 \, (-2080^\circ), \ 232.5 \, (-2050^\circ), \ 210 \, (12750^\circ).\)

\(\alpha\, (-)-2\,'-\text{Methoxy}-2,5,9\,-\text{trimethyl}-6,7\,-\text{benzomorphan}\cdot\text{HBr} \, (7c).\)

\(\text{UV} \ (\epsilon \ 3.39 \times 10^{-4}): \ 287 \, (2040), \ 279 \, (2200), \ 227 \, (8000), \ 219.5 \, \text{inf} \, (6960). \) Fig. 18.

\(\text{CD} \ (\epsilon \ 1.10 \times 10^{-4}): \ 296 \, (0^\circ), \ 287 \, (-3900^\circ), \ 283 \, (-3490^\circ), \)
278 (-4110°), 256 (0°), 245 (0°), 228 (+9940°), 217 (0°), 210 (-4320°). Fig. 18.

RD (c 3.39x10^-5): 325 (-1240°), 290 (-4320°), 286.5 inf (-2360°), 277.5 (0°), 265 (+1270°), 247.5 (+470°), 235.5 (+2650°), 232 (0°), 229 inf (-3300°), 216 inf (-15600°), 210 (-16700°). Fig. 18.

RD (R) (c 1.29x10^-4): 287 (-4190°), 275 (0°), 270 (+1100°), 250 (+155°), 237 (+1400°).

**NH₄OH added:**

UV (c 1.36x10^-4): 267 (2040), 279 (2250), 227 (7080), 220 (6860).

CD (c 4.42x10^-5): 297 (0°), 282 (-5020°), 247 (0°), 238 (0°), 226 (+4140°), 217.5 (0°), 210 (-7750°).

RD (c 1.36x10^-5): 325 (-1470°), 291 (-4560°), 287 inf (-2280°), 283 inf (-2130°), 276 (0°), 266 (+882°), 250 (0°), 245 (-515°), 240 (-740°), 209 (-19400°), 206 (0°).

RD (R) (c 1.29x10^-4): 287 (-3780°), 278 (0°), 270 (+1470°), 251 (+150°), 240 (+775°).

α-(+)-2'-Hydroxy-2-methyl-5,9-diethyl-6,7-benzomorphan (7d).

**Free base:**

UV (c 2.54x10^-4): 288 sh (1980), 282 (2260), 228 sh (5470), 220 (5960).

CD (c 1.32x10^-4): 304 (0°), 290 sh (+3330°), 282.5 (+3820°), 251 (0°), 243 (0°), 228 (-1810°), 218 (0°), 210 (+9700°). Fig. 20.

RD (c 5.28x10^-5): 325 (+1290°), 294 (+3880°), 288 inf (+2100°), 279 (0°), 272.5 (-606°), 263 (0°), 245 inf
+2000°, 227 inf (+9000°), 215 (+17500°).

RD (R) (c 1.13x10⁻³): 290 (+3450°), 280 inf (+1950°), 276 (0°), 274 (-442°), 268 (0°), 245 (+1770°).

HCl added:

UV (c 2.54x10⁻⁴): 288 sh (2010), 281 (2260), 227.5 (6100), 221 (5910).

CD (c 6.60x10⁻⁵): 300 (0°), 289 sh (+3260°), 282.5 (+3730°), 277.5 sh (+3300°), 256 (0°), 242 (0°), 232 (-5900°), 230.5 (-5630°), 228 (-6300°), 218 (0°), 216 sh (+1770°), 210 (+3700°). Fig. 20.

RD (c 2.54x10⁻⁵): 325 (+1260°), 294 (+4060°), 278 (0°), 272.5 (-825°), 258 (0°), 245 (+826°), 237 (+200°), 213 sh (+18000°), 210 (+22000°).

α-(-)-2'—Hydroxy-2-methyl-5,9-diethyl-6,7-benzomorphan (7d).

UV (c 2.52x10⁻⁴): 288 sh (2050), 281.5 (2330), 228 sh (5710), 220 (6245).

CD (c 1.31x10⁻⁴): 302.5 (0°), 291 sh (-3300°), 283 (-3910°), 252 (0°), 238 (0°), 228 (+1180°), 220 (0°), 217.5 sh (-470°), 215 (-1500°).

RD (c 5.04x10⁻⁵): 325 (-2840°), 294 (-3910°), 278 (0°), 270 (+735°), 261 (0°), 235 inf (-2980°), 215 (-15600°).

RD (R) (c 5.90x10⁻⁴): 293 (-3970°), 285 inf (-2450°), 278 (0°), 270 (+250°), 259 (0°), 240 (-2540°).

HCl added:

UV (c 2.52x10⁻⁴): 287.5 (2140), 280.5 (2400), 227 (6460), 220 (6300).
CD (c 6.56x10^{-5}): 299 (0°), 292 sh (-3400°), 282 (-4780°), 246 (0°), 241 (0°), 230 (+4700°), 221 (0°), 214.5 (-3280°), 212.5 (-3320°), 210 (-4230°).

RD (c 2.52x10^{-5}): 325 (-1270°), 294 (-4040°), 286 inf (-1940°), 283 inf (-1590°), 279 (0°), 272 (+1000°), 257 (0°), 242 (-755°), 237 (-357°), 221 (-13000°), 217.5 (-13300°), 215 (-15000°).

8-(−)-2'-Hydroxy-2-methyl-5,9-diethyl-6,7-benzomorphan (7e).

UV (c 1.94x10^{-4}): 288 sh (2010), 282 (2310), 230 inf (5310), 221 (6460).

CD (c 1.26x10^{-4}): 306 (0°), 292.5 sh (-3030°), 284.5 (-3850°), 254 (0°), 253 (0°), 227.5 (+2880°), 216 (0°), 210 (-4900°). Fig. 21.

RD (c 4.86x10^{-5}): 325 (-1950°), 295 (-4420°), 274.5 (0°), 270 (+226°), 262 (0°), 255 inf (-308°), 240 inf (-1130°), 210 (-11000°).

RD (R) (c 1.96x10^{-3}): 288 (-2420°), 276 (0°), 263 (+1150°), 240 (+765°).

HCl added:

UV (c 1.94x10^{-4}): 288 sh (2125), 281.5 (2370), 227.5 sh (6080), 220.5 (6315).

CD (c 5.04x10^{-5}): 297.5 (0°), 283 (-4630°), 260 (0°), 240.5 (0°), 228 (+3140°), 215 (+1800°), 210 (+2520°). Fig. 21.

RD (c 1.94x10^{-5}): 325 (-927°), 294 (-3810°), 282 (0°), 270 (+1700°), 252 (+875°), 237 (+3680°), 231 (0°), 218 (-8960°), 213 (-8650°), 207.5 (-8900°).

α-(−)-2'Hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan·HBr (7f).
UV (c 1.67x10^-4): 288 sh (2050), 281 (2320), 263.5 sh (920), 257.5 sh (645), 252 sh (454), 247 sh (358), 227.5 (6300).

CD (c 1.47x10^-5): 298 (0°), 291 sh (-3120°), 282 (-3900°), 256 (0°), 244 (0°), 228 (+4910°), 272 (0°), 220 (-1650°). Fig. 22.

RD (c 3.35x10^-5): 325 (-2460°), 294 (-6400°), 284 inf (-3480°), 272.5 (-1150°), 240 inf (-5050°), 236.5 inf (-5450°), 224 inf (-18000°), 211 inf (-29700°), 210 (-33000°). Fig. 23.

NH₄OH added:

UV (c 1.67x10^-4): 288.5 sh (1990), 281.5 (2240), 267.5 sh (1090), 264 (825), 257.5 (549), 252 sh (394), 229 inf (6140).

CD (c 6.73x10^-5): 298 (0°), 289 (-3600°), 287 (-3480°), 284 (-3960°), 282.5 (-3830°), 281 (-3960°), 255 (0°), 241.5 (0°), 231 (-2940°), 225 (-1800°), 215 (-10600°). Fig. 22.

RD (c 1.68x10^-5): 325 (-2560°), 294 (-5540°), 282.5 inf (-3090°), 275 (-1190°), 235.5 (-9460°), 231 (-8930°), 215 (-23000°). Fig. 23.

α-(+)-2′-Methoxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphaphan•HBr (7q).

UV (c 1.75x10^-4): 2.86 (2020), 278.5 (2170), 264 sh (943), 257.5 sh (595), 251.5 (360), 247 inf (200), 227 (8550).
CD (c 7.26x10^-5): 296 (0°), 288 (+3500°), 283.5 (+3150°), 279.5 (+3700°), 258 (0°), 238 (0°), 231 (-4100°), 223 (0°), 210 (+18000°).

RD (c 1.75x10^-5): 325 (+2510°), 290.5 (+6400°), 284.5 (+4220°), 282.5 (+4700°), 269 (+855°), 243 (+5420°), 224 inf (+20000°), 217 inf (+25000°), 215 (+27000°).

RD (c 1.22x10^-4): 285 (+6230°), 272 (+1470°), 239 (+5940°), 236 (+5400°).

NH₄OH added:

UV (c 1.75x10^-4): 287.5 sh (2060), 280 (2270), 267.5 sh (1263), 264 sh (943), 258.5 sh (668), 253 sh (451), 228 sh (8030).

CD (c 7.26x10^-5): 293.5 (0°), 287.5 (+3100°), 284 (+2980°), 281 (+3960°), 254 (0°), 247 (0°), 228 (+4740°), 227 (+4420°), 215 (+10900°).

RD (c 1.75x10^-5): 325 (+2340°), 293 (+5720°), 283 inf (+3660°), 271.5 (+1030°), 232.5 (+10600°), 227.5 (+9820°), 215 (+18500°).

α-(-)-2'-Methoxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan-HBr (7q).

UV (c 1.59x10^-4): 285.5 (2100), 275.5 (2300), 263.5 sh (1079), 257.5 sh (738), 252 sh (480), 227 (8510).

CD (c 6.61x10^-5): 296 (0°), 287.5 (-3840°), 284 (-3650°), 279 (-4100°), 257 (0°), 237.5 (0°), 229 (+3280°), 223 (0°), 217 (-11000°), 215 (-10300°), 213 (-11900°).

RD (c 1.58x10^-5): 325 (-2400°), 290 (-6140°), 287 inf (-4430°), 271 (-1140°), 236 inf (-6450°), 217.5
(-26000°), 216 (-25100°), 215 (-26600°).

RD (R) (c 1.45x10⁻⁴): 288 (-5800°), 268 (-1970°), 236 (-5240°).

NH₄OH added:

UV (c 1.59x10⁻⁴): 297.5 (2120), 279.5 (2370), 268 sh (1420), 264 sh (1100), 258 sh (756), 252.5 sh (542), 226 (7950).

CD (c 6.61x10⁻⁵): 297 (0°), 288 (-3590°), 286 (-3220°), 280 (-4030°), 256 (0°), 247 (0°), 231 (-5740°), 225 (-5550°), 218 (-10700°), 217 (-9810°), 215 (-11800°).

RD (c 1.58x10⁻⁵): 325 (-2020°), 291 (-6070°), 270 (-1840°), 233 (-11000°), 230 (-10500°), 215 (-21000°).

(-)-2'-Hydroxy-5,9-diethyl-6,7-benzomorphan (7h).

UV (c 2.01x10⁻⁴): 288 sh (2200), 282 (2500), 227 sh (6420), 221 (6510).

CD (c 4.92x10⁻⁵): 300 (0°), 285 (-3540°), 255 (0°), 238 (0°), 229 (+3840°), 221.5 (0°), 216.5 (-2940°), 215 (-2440°).

RD (c 5.02x10⁻⁵): 330 (-995°), 293 (-3140°), 283 inf (-1230°), 272 (-60°), 242.5 (-1800°), 238 (-1700°), 220 inf (-13000°), 210 (-22000°).

HC1 added:

UV (c 2.01x10⁻⁴): 288.5 sh (2280), 281 (2640), 227.5 (7020), 220.5 (6840).

CD (c 4.92x10⁻⁵): 298 (0°), 283 (-3500°), 257 (0°),
240.5 (0°), 229 (+5000°), 218 (0°), 214 (-2400°), 212 (-2250°), 210 (-3700°).

RD (c 2.00x10^{-5}): 325 (-1350°), 293 (-4000°), 277 (0°), 271 (+350°), 263.5 (0°), 242.5 (-1500°), 238 (-1100°), 220 inf (-13000°), 210 (-22000°).

Low Wave Length ORD and CD Spectra of \(\beta\)-(\(-\))-2'-Hydroxy-2,5,9-trimethylbenzomorphan Hydrobromide (7b). The nitrogen flow into the Cary 60 was greatly increased to purge residual amounts of air from the instrument. A good baseline (water) was obtained in both the ord and cd modes from 330-195 nm. Somewhat less reliable, but tolerable, baselines were obtained between 195 and 185 nm. The ord, initial concn 1.45x10^{-4} mol/100 ml, and the cd, initial concn 4.52x10^{-5} g/cc, spectra were determined from 330 to 186 nm. The data are recorded as nm ([\(\Phi\)]) and nm ([\(\Theta\)]).

\(\beta\)-(\(-\))-2'-Hydroxy-2,5,9-trimethyl-6,7-benzomorphan-HBr (7b)

CD (c 4.52x10^{-5}, H2O): 296 (0°), 286.5 (-3150°), 282.5 (-2900°), 279 (-3520°), 256 (0°), 241 (0°), 225.5 (+7250°), 213.5 (0°), 210 (-1570°), 206 (0°), 203.5 (+1570°), 202 (0°); (c 1.81x10^{-5}): 240 (0°), 225.5 (+7250°), 213.5 (0°), 209 (-1900°), 206 (0°), 203.5 (+1380°), 202 (0°); (c 3.62x10^{-6}): 202 (0°), 194 (-54700°), 192 (-47000°), 188 (-54700°), 185 (0°). Fig. 24.

RD (c 1.45x10^{-4}, H2O): 330 (-872°), 290 (-3130°), 285 inf (-2070°), 283 inf (-1590°), 280 inf (-1010°), 276 (0°), 267 (+672°), 253 (0°), 247.5 (-166°), 242 (0°), 233 (+1110°), 229 (0°); (c 5.79x10^{-6}): 229 (0°),
225 \text{inf} (-6040^\circ), 222.5 \text{inf} (-7930^\circ), 218 \text{inf} (-12200^\circ),
210 \text{inf} (-12900^\circ); (\leq 1.16 \times 10^{-6}); 206.5 (-15500^\circ),
197.5 (-51700^\circ), 191 (0^\circ), 187.5 \text{inf} (+25000^\circ), 186
(+27600^\circ). \text{Fig. 24.}
SUMMARY

The 6,7-benzomorphan (7) analog, 3-methyl-6,7-benzo-3-azabicyclo[3.3.1]nonen-9-one (31) (nitrogen at position 3 instead of 2), was prepared via the Mannich reaction with \( \beta \)-tetralone, \( \text{CH}_3\text{NH}_2 \) and HCHO. Resolution was accomplished with (+)-tartaric acid. The uv, ord, and cd spectra were determined in various solvents and are discussed. The uv spectra give evidence of homoconjugation of the \( \beta,\gamma \)-unsaturated ketone (\( \lambda_{290} \), \( \epsilon_{1170} \)), but ord and cd spectra give little support to this (\( \epsilon_{304}^{\text{EPA}} +572^0 \)).

An alternate synthetic route to 3-methyl-6,7-benzo-3-azabicyclo[3.3.1]nonene (17) was attempted, the first step being an aldol condensation of 1-methyl-4-piperidone and benzaldehyde. This gave both geometrical isomers of 1-methyl-3-benzyl-4-piperidone (15); both isomers exist preferentially in the enol form. Attempted reduction of 15a to 1-methyl-3-benzyl-4-piperidinol (16) by several routes gave products which appeared to trap or occlude hydrocarbon solvents from which they could be separated only by strong heating. Attempted cyclization of 16 to 17 with PPA and with \( \text{P}_4\text{O}_{10} \) gave only unsaturated products.

The ord, cd, and uv spectra of a series of derivatives of 6,7-benzomorphan (7) were recorded for the free bases and hydrohalide salts. In a normal cd spectrum the compounds exhibit a long wave length Cotton effect near 280 nm and a second, antipodal Cotton effect near 230 nm.
The only exceptions were the base forms of the phenethyl derivatives 7f and 7g in which the 230 nm band was of "abnormal" sign. The ord and cd spectra of 7b,H9r were recorded from 325-185 nm. In both modes an intense Cotton effect was observed at 188 nm (\([\Theta]_{\text{max}} -54000^0\)).

A sector rule for the phenyl chromophore was postulated for the long wave length Cotton effect at 280 nm. This was applied to a number of morphinan and morphine derivatives and gave correct predictions in every case.
APPENDIX

The $\theta$-line rotations of several of the 6,7-benzo- morphan derivatives discussed in this thesis have not been reported in the literature. Below are listed literature values and values taken from ord spectra from the Cary 60. $\left[\alpha\right]_{546}$ values are also reported; the concentrations ($\eta/100 \text{ ml}$), all in methanol, are the same for both values.
<table>
<thead>
<tr>
<th>Compound</th>
<th>([\alpha]_D) (lit.)</th>
<th>([\alpha]_D) Cary 60</th>
<th>([\alpha]_{546}) Cary 60</th>
<th>Concn</th>
</tr>
</thead>
<tbody>
<tr>
<td>((-\text{-7a})) (base)</td>
<td>-84.8° (c 0.09, EtOH)(^d)</td>
<td>-108°</td>
<td>-129°</td>
<td>0.146</td>
</tr>
<tr>
<td>((-\text{-7b})) (HBr)</td>
<td>-47.2° (c 0.9, H(_2)O)(^a)</td>
<td>-59°</td>
<td>-72°</td>
<td>0.202</td>
</tr>
<tr>
<td>((-\text{-7c})) (HBr)</td>
<td>-50.5° (c 1.1, H(_2)O)(^b)</td>
<td>-64°</td>
<td>-72°</td>
<td>0.110</td>
</tr>
<tr>
<td>((+\text{-7d})) (base)</td>
<td>+59.0° (c 0.55, EtOH)(^c)</td>
<td>+63°</td>
<td>+76°</td>
<td>0.165</td>
</tr>
<tr>
<td>((-\text{-7d})) (base)</td>
<td>-61.5° (c 0.55, EtOH)(^c)</td>
<td>-63°</td>
<td>-77°</td>
<td>0.328</td>
</tr>
<tr>
<td>((-\text{-7e})) (base)</td>
<td>-56.8° (c 2.5, MeOH)(^b)</td>
<td>-68°</td>
<td>-78°</td>
<td>0.126</td>
</tr>
<tr>
<td>((-\text{-7f})) (HBr)</td>
<td>-81.4° (c 1.12, EtOH)(^d)</td>
<td>-97°</td>
<td>-114°</td>
<td>0.165</td>
</tr>
<tr>
<td>((+\text{-7g})) (HBr)</td>
<td>+78.6° (c 1.6, EtOH)(^b)</td>
<td>+92°</td>
<td>+117°</td>
<td>0.182</td>
</tr>
<tr>
<td>((-\text{-7g})) (HBr)</td>
<td>-80.1° (c 2.1, EtOH)(^b)</td>
<td>-85°</td>
<td>-106°</td>
<td>0.165</td>
</tr>
</tbody>
</table>

\(^b\) E. L. May, unpublished results.


50. G. G. DeAngelis, ibid., p 129.


53. G. G. DeAngelis, ibid., p 130.

54. G. G. DeAngelis, ibid., p 132.

55. G. G. DeAngelis, ibid., p 131.

56. G. G. DeAngelis, ibid., p 133.

