THE SYNTHESIS OF 8-AZASTEROIDS

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THE SYNTHESIS OF 8-AZASTEROIDS

BY

GEORGE A. HEAVNER
A. B., GETTYSBURG COLLEGE

A THESIS
Submitted to the University of New Hampshire
In Partial Fulfillment of
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Graduate School
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This thesis has been examined and approved.

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This thesis is dedicated to my wife Linda.
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ABSTRACT

THE SYNTHESIS OF
8-AZASTEROIDS

by

GEORGE A. HEAVNER

A new total synthesis of 8-azasteroids has been achieved. The key step involved the alkylation of enaminoketones (27), formed quantitatively from 1,3-cyclopentadione and substituted β-phenethylamines, in such a way as to form the C-ring and provide a suitable functional group to allow formation of the B-ring by cyclization. β-Propiolactone accomplished this transformation in high yields.

The Bischler-Napieralski cyclodehydration of these compounds (50) in hot polyphosphoric acid gave quantitative yields of two unexpected products, 56 and 57, in equal amounts. Alkylation and reduction of these compounds gave several new 18,19-dinor-8-azasteroids. The reduction of the O-methyl salt of the enaminoketone 58 gave, in addition
to the expected product $\mathbf{52}$, a product arising from a novel 1,4-hydride reduction. All attempts to introduce an 18-alkyl substituent were unsuccessful.

\[ \text{Diagram of compounds 56, 57, 58, and 83} \]
SECTION I
INTRODUCTION

Prior to 1963 all steroids containing nitrogen in the skeleton were synthesized from naturally occurring steroids, and none of these azasteroids contained a nitrogen atom common to two rings.¹ These azasteroids and aza-homosteroids were synthesized by opening one of the natural steroid rings and inserting a nitrogen function followed by ring closure, or by ring expansion and rearrangement reactions with nitrogen introduction.²,³

The first total synthesis of an azasteroid was reported by Meltzer and coworkers⁴-⁶ in 1963 and was rapidly followed by other syntheses from the laboratories of Meyers⁷-¹⁰, Clarkson¹¹,¹², Huisman¹³-¹⁸ and others.¹⁹-²³ The majority of these azasteroids have nitrogen at the 8-position and can therefore utilize synthetic methods applicable to the synthesis of partially reduced isoquinolines to close the B ring (¹.a) or use the basicity of the nitrogen in partially reduced isoquinolines for closing of the C ring (¹.b).

The synthesis of Meltzer and coworkers proceeded through the intermediate 6 (Scheme 1), which was prepared from 2-methyl-1,3-cyclo-
pentadione by alkylation with acrylonitrile, followed by hydrolysis to the acid to give 4. Condensation of this intermediate with 3-methoxy-\(\beta\)-phenethyl amine and reduction of the 14,15-double bond gave 6. A Bischler-Napiersalski cyclodehydrative closure of the B ring gave the desired 8-azasteroid, isolated as the perchlorate salt. The overall yield, starting with 2 was 27% in 4 steps (5 operations) with a 14% conversion. Separation of the isomers created in the reduction to 6 and of the reduction of the 8,9-double bond in 2 gave three of the four possible isomers - 9\(\alpha\),13\(\alpha\),14\(\alpha\)-, 9\(\alpha\),13\(\beta\),14\(\alpha\)-, and 9\(\alpha\),13\(\beta\),14\(\beta\)-.
The synthetic routes of Meyers and Clarkson are similar in that they both make use of partially reduced isoquinolines. Meyers' synthesis involves the alkylation of the enamine system (Scheme 2, 2) as the key step to give the 12-keto steroid 10. An analogous alkylation using an alkyl halide instead of an acyl group for reaction with the enamine formed with 2-methyl-1,3-cyclopentadione gave the 17-keto series (Scheme 3). This scheme generates an enaminoketone system (13) which can be alkylated under forcing conditions. The difficulty in the alkylation of this system is exemplified by the observation that if 2-methyl-1,3-cyclopentadione is substituted for cyclopentanone in Scheme 2, the resulting enaminoketone system cannot be cyclized to give the desired 12,17-diketo-8-azasteroid. Yields for these reactions are 70% for 10 (Scheme 2) and 43% for 15 (Scheme 3) starting from the tetrahydroisoquinolines.
The route used by Clarkson and coworkers\textsuperscript{11,12} was similar to that of Meyers in that a 1-substituted, partially reduced isoquinoline was used as an intermediate and the alkylation of an enaminoketone was required. In this instance, however, a 3,4-dihydroisoquinoline (Scheme 4, 19) was used and the condensation and cyclization from 19 to 20 appeared to be concerted. The 8-azasteroid 20 was produced in an overall crude yield of 42\% from 16 and this synthesis had the advantage that the product had only one asymmetric center present in the molecule.

Recently another synthesis of an 8-azasteroid was reported\textsuperscript{20} which used 3,4-dihydroisoquinoline and cyclic triketones (Scheme 5). This synthesis gave moderate yields of 56\% of 23 in one step and was shown to be successful with several triketones.
These syntheses have resulted in 8-azasteroids with several potential sites for modification. From them have been prepared 8-aza-19-norprogesterone (24), 8-aza-19-nortestosterone (25), 8-azaestrone (26) and derivatives of these corresponding to those carbocyclic compounds which are pharmacologically important.

8-Azaestrogens have shown limited estrogenic activity.\textsuperscript{24} 17α-Ethynyl-3-methoxy-8-azaestra-1,3,5(10)-trien-17β-ol (27) had 1/20 the estrogenic activity of the carbocyclic analog, Mestranol.\textsuperscript{12} X-Ray studies\textsuperscript{24,25} have shown that the introduction of a nitrogen into the 8-position does not significantly alter the molecular dimensions of the steroid ring system. It has been suggested that the basicity of the nitrogen, and not its geometry, is responsible for the decrease in
activity since the basic center offers a competitive site to the oxygen for protonation and may interfere with glucuronidation at the 3-position.

The 8-aza-19-norpregesterone has been reported to be inactive at 5 mg/kg/day, fully active at 50 mg/kg/day and active at 1/40 the activity of 19-norpregesterone (subcutaneous) by the Clauberg-McPhail assay, and toxic at 4 mg/rat/day. Very little oral activity was noted. The 13-ethyl-8-aza-19-norpregesterone showed activity (subcutaneous) almost equivalent with 19-norpregesterone. The introduction of either a 17α- or 17β-hydroxyl group gave compounds inactive at 5 and 25 mg/kg/day (subcutaneous).

8-Aza-19-nortestosterone was devoid of progestational activity (Clauberg-McPhail assay), while the 17α-ethynyl derivative had activity 1/5 that of the equivalent carbocyclic compound. In 19-nortestosterone any increase in the size of the 13-substituent enhances androgenic/anabolic activity. The 8-aza-19-nortestosterone, the 13-ethyl, and 13-ethyl-17α-ethyl derivatives exhibited almost no androgenic/anabolic activity. The androgenic dose for 13-ethyl-17α-ethyl-8-aza-19-nortestosterone was 100 times that of testosterone propionate.

Several compounds related to azasteroids have been tested for antifertility activity and some of these results have been encouraging.

8-Azasteroids have also been found to be active as skeletal muscle strengtheners and as anti-shock agents.

A large number of azasteroids, containing one or more nitrogens at various sites in the steroid nucleus, have been synthesized. These compounds are of interest for their potential clinical value. Analogs of carbocyclic steroids, known to possess hormonal activity,
have been prepared in the hope that the nitrogen would increase either π-bonding or hydrogen bonding characteristics between the molecule and the receptor site or enhance the bonding differential between competitive receptor sites.\(^{32}\)

In addition to azasteroids as potential progestational, androgenic or anabolic agents, azasteroids have been investigated as antineoplastic agents, inhibitors of cholesterol biosynthesis, analgesics\(^ {33}\) and antimicrobial agents.\(^ {34}\)

The mode of action in these cases may be related to the effect of the azasteroid on the DNA control of RNA synthesis. It has been postulated that steroid hormonal action is exerted by a mechanism of this type.\(^ {32}\) Regardless of whether the site of action is on DNA, proteins or other biomolecules, the modification of steroids by the introduction of nitrogen into the steroid nucleus has the potential for generating potent pharmacological agents by modification of the binding between the agent and the receptor site without causing gross structural deviations from the geometry of the carbocyclic steroid nucleus which could adversely affect the biological activity.
SECTION II
RESULTS AND DISCUSSION

A. General Approach to the Synthesis of 8-Azasteroids

The approach to the synthesis of 8-azasteroids (Scheme 6) to be investigated in this study, required, as the key step, the alkylation of the enaminoketone formed from a primary amine and cyclopentane-1,3-dione. The alkylating agent must provide the three carbon fragment which would also form a lactam. Specifically the transoid enaminoketone system 28 would be transformed into the lactam 29. The cyclodehydration of these dihydropyridones should yield the multifunctional 8-azasteroids 30.

The problems associated with the planning of this synthetic approach to 30 were the lack of data concerning enaminoketones prepared from primary amines, the difficulty in the alkylation of enaminoketones reported by several workers, and the unexplored cyclodehydration of dihydropyridones to give the proposed dihydropyridinium salts.
Scheme 6
B. Synthesis of Enaminoketones

The literature contains few examples of enamines prepared from other than secondary amines. The tendency of enamines prepared from primary aliphatic amines or ammonia, lacking any stabilizing influence, to exist predominately in the tautomeric iminium form (32) makes them highly susceptible to hydrolysis and therefore inherently unstable. It was known that enamines of both α- and β-dicarbonyl compounds are formed readily and that the vinyl nitrogen system remains in conjugation with the second carbonyl function. Enamines formed from these dicarbonyl compounds are stable whether the amine is primary, secondary or ammonia.

Ultraviolet and nuclear magnetic resonance spectra and dipole moment studies on the enamines prepared from β-dicarbonyl compounds have shown them to exist in the enaminoketone form (33).

\[ \text{31} \quad -\text{C} = \text{C} - \text{N} - \quad -\text{C} - \text{C} = \text{N} - \quad \text{32} \]

\[ 0 = \text{C} - \text{C} = \text{C} - \text{N} - \quad \text{33} \]

The preparation of these compounds dates back to 1885 when Fischer and Bülow isolated a stable crystalline compound from the reaction of benzoylaceton and ammonia.\(^{35}\) Prior to 1946 no enamines were reported of any cyclic β-dicarbonyl compounds.\(^{36}\)

Those cyclic systems which have been studied most are the 5,5-dimethyl-1,3-cyclohexadione and 1,3-cyclohexadione. In 1962 Dudek and coworkers treated 5,5-dimethyl-1,3-cyclohexadione with methyl amine, benzyl amine and 2,2,2-trifluoroethylamine to give the stable enaminoketone-
ketones. The reaction of ammonia with 1,3-cyclohexadione yielded the primary enaminoketone. These enaminoketones can be prepared by the action of the appropriate amine on either the β-diketone or its mono enol ether. Few instances are reported in which an enaminoketone is formed from a five membered cyclic diketone and an amine other than a secondary amine. The mono enol ethyl ether of 1,3-cyclopentadione was heated in an autoclave with a saturated solution of ammonia in ethanol to give a quantitative yield of 3-amino-cyclopent-2-ene-1-one.

\[
\begin{align*}
\text{34} & \quad \text{35} & \quad \text{36}
\end{align*}
\]

1,3-Cyclopentadione was prepared in excellent yield from cyclopent-4-ene-1,3-dione, which was readily available from dicyclopentadiene by an established procedure. The reduction of the double bond was accomplished over W-2 Raney Nickel according to the procedure outlined by Zymalkowski and coworkers. The reaction of the saturated diketone with substituted β-phenethyl amines in benzene gave the enaminoketones and in quantitative yield. Isolation of these compounds by evaporation of the solvent gave material of sufficient purity for succeeding reactions.

Both of the enaminoketones were crystalline solids which exhibited absorption in the infrared region at approximately \(3300 \text{ cm}^{-1}\).
for the N-H stretching vibration and several absorptions in the area of 1610 to 1650 cm\(^{-1}\) for the enaminoketone moiety. Dabrowski and Dabrowska investigated the infrared absorptions of enaminoketones and observed that the cisoid compounds exhibited two prominent absorptions at approximately 1560 and 1650 cm\(^{-1}\) while the transoid compounds exhibited several bands from 1560 to 1600 cm\(^{-1}\). Although no infrared data are available in the literature for enaminoketones formed from 1,3-cyclopentadiones, the absorption bands between 1610 and 1650 cm\(^{-1}\) are reasonable and in agreement with the data of Dabrowski and Dabrowska, considering that a shift to higher frequency of 25 to 35 cm\(^{-1}\) would be expected on changing from a 6- to a 5-membered cyclic ketone.

The enaminoketones 37a and 37b exhibited absorptions in the ultraviolet region at 271 nm (log\(\varepsilon = 4.50\)). The similarity in ultraviolet
spectra for the two compounds was expected since the only difference between the two compounds was the substitution of the aromatic ring. The low molar absorptivities of anisole (3.34 at 272 nm) and veratrole (3.4 at 274 nm) would not be expected to affect significantly the ultraviolet spectra of 37a and 37b.42

The proton magnetic resonance spectra of the enaminoketones 37a and 37b exhibited singlets at approximately δ 5.0 for the vinyl hydrogens. The N-H protons appeared as broad bands, the position of which was concentration dependent, generally between δ 6.0 and δ 8.0. In both compounds the ethylene protons of the cyclopentenone ring appeared as complex multiplets. The methylene protons adjacent to the nitrogen showed coupling not only with the adjacent methylene protons but also with the proton on the nitrogen. The pattern collapsed to an A₂B₂ pattern on irradiation of the N-H proton.
C. Synthesis of N-(\(\beta\)-phenethyl)-1,2,3,4-tetrahydro-pyridan-2,5-diones

The alkylation of enaminoketones (40) or vinylogous amides poses several difficulties in that there are three possible sites for alkylation - at carbon, at nitrogen or at oxygen. Compounding this difficulty is the lack of a thorough, systematic study of the alkylation of enaminoketones, and specifically a lack of information about the alkylation of enaminoketones formed from primary amines and cyclic diketones. In addition there are several reports of anomalies and failures where none were expected in the alkylation of enaminoketones.

\[
\begin{align*}
\text{N} & \quad \text{C} = \text{C} - \text{C} = \text{O} \\
\text{O} & \\
\end{align*}
\]

The enaminoketones formed from 5,5-dimethyl-1,3-cyclohexadione and cyclohexylamine (41) gave only O-alkylation with methyl iodide.\(^{43}\) A similar system (42) formed from 1,3-cyclohexadione and cyclohexylamine was alkylated with methyl iodide using sodium hydride in tetrahydrofuran to give 14\% of the N-methyl derivative and an unspecified amount of the C-alkylated product.\(^ {44}\)

Alkylation of the acyclic system formed from acetyl acetone and pyrrolidine (42) gave C-alkylation with methyl iodide but O-alkylation with ethyl iodide.\(^ {45}\) The enaminoketones formed from ammonia and 1,3-cycloalkanones (44) reacted with propargaldehyde to yield the pyridine derivatives \(^ {45,29}\) A mechanism involving C-alkylation of the
enamine moiety has been postulated but other mechanisms not involving C-alkylation as the first step are possible.

A stereochemical dependence has also been observed in the alkylation of enaminoketones. Meyers and coworkers have observed that cisoid enaminoketones have varying amounts of O- and C-alkylated products depending on solvent and reaction time. All transoid systems gave exclusively O-alkylated products regardless of the reaction conditions. With this background the conditions to be used for the alkylation of were designed.

The reagent used to form what is to be the C-ring must be bifunctional, capable of alkylating the enaminoketone at carbon and then capable of cyclizing with the nitrogen, or alternatively of
reacting with the amine followed by alkylative cyclization. The reaction must also provide the C-ring with a suitable functional group to allow cyclization to form the B-ring.

In their synthesis of lycopodium alkaloids, Wiesner and coworkers succeeded in causing the reaction of the enaminoketone 46 with acrylic acid to give a high yield of the lactam 47.\(^4\) The reaction of the enaminoketone 48 with acrylic acid under conditions identical with those used by Wiesner gave only recovered starting material. This may be a result of the geometric constraints of compound 46 not present in 48.

\[
\begin{align*}
&46 & & 47 \\
&\text{H-N} & & \text{O} \\
&\text{O} & & \text{N} \\
\end{align*}
\]

Although enamines are readily alkylated with acrylonitrile, the reaction of 48 with acrylonitrile under a variety of conditions gave no recoverable products other than starting material. Ethyl acrylate also gave no reaction. The failure of the latter reagent was not surprising in view of the fact that 2-methyl-1,3-cyclopentadione was found to resist Michael addition to ethyl acrylate although it gave an adduct with acrylonitrile.\(^6\)

Compound 48 was treated with acrolein and acrolein dimethyl acetal under a variety of conditions ranging from room temperature to high temperature sealed tube reactions in an attempt to produce
N-(β-3,4-dimethoxy-phenethyl)-1,4-dihydro-pyridan-5-one. This dihydropyridine derivative should undergo cyclization under acidic conditions to yield the azasteroids, but all reactions with these reagents were unsuccessful.

The use of the highly reactive dimethyl acetylene dicarboxylate gave multiple additions, as evident from the multiple singlets due to methoxyl signals in the pmr of the crude reaction mixture. Attempts to separate the desired product from the reaction mixture were unsuccessful. This reagent is known to give 2+2 cycloadditions with enamines and enamino ketones to yield cyclobutenes which can undergo rearrangement and ring expansion.49

The reaction of β-chloropropionic acid with 48 gave nearly quantitative recovery of starting material. In view of the difficulties encountered by Meyers and coworkers in causing the intramolecular alkylation of the enamino ketone 49, the failure of obtaining a reaction with 48 was not surprising.8

β-Propiolactone is a three carbon, highly reactive compound which is known to alkylate enamines of cyclic ketones to give the 2-keto-
cycloalkyl propionamides. The reactivity of this reagent with enamines formed from primary amines or with enamino ketones had not previously been explored. β-Propiolactone proved unreactive with the enamino kton 48 in benzene and toluene. However, when chlorobenzene was used as the solvent, water was observed in the reaction mixture after 2 to 3 days. The water was removed as the azeotrope with chlorobenzene and an equivalent amount of dry chlorobenzene was added. This procedure was followed daily for 7 days, at which time the formation of additional water was not evident. Evaporation of the solvent followed by chromatography on neutral alumina and recrystallization of the resulting solid afforded a good yield of the desired lactam 50b. In an effort to improve the yield and decrease the time of the reaction of 48 with β-propiolactone, the anion of the enamino kton was generated with sodium hydride (evidenced by hydrogen evolution) and to this was added the β-propiolactone. Work-up of this reaction gave a good yield of

\[
\begin{array}{c|cc}
R_1 & R_2 \\
50a & H & CH_3O \\
50b & CH_3O & CH_3O \\
\end{array}
\]
starting material. It was found that by using a mixture of xylenes as solvent instead of chlorobenzene the yield was not substantially affected; however, the reaction time was decreased to 20 hours. The use of the higher boiling solvent required a larger excess of the β-propiolactone since substantial amounts of polymer were formed in the condenser.

The dihydropyridone 50a was prepared in an identical manner to that used to prepare 50b.

The dihydropyridones 50 exhibited spectral properties consistent with the proposed structure. The infrared spectra exhibited absorptions at 1620 and 1670 cm⁻¹ for 50a and 1640 and 1680 cm⁻¹ for 50b. The 3- and 4-protons in both compounds appeared as singlets in the pmr. The pmr spectra clearly showed the A₂B₂ pattern for the aliphatic protons of the phenethyl group and aromatic patterns consistent with the respective substitution patterns.

The ultraviolet absorption spectra exhibited maxima at 291 nm (logε = 4.20) and 282 nm (logε = 4.20) for 50a and 299 nm (logε = 4.20) for 50b. There appears to be no immediately obvious explanation for the slight difference in spectra between the two systems, although an interaction of the ketodihydropyridone system with the aromatic rings could account for the slight shift in absorption maxima.
D. Cyclization of the Dihydropyridones

The Bischler-Napieralski cyclodehydration reaction has proven to be an excellent method for the synthesis of 3,4-dihydroisoquinolines even though some failures have been reported. This method of ring closure has been used successfully in several of the published reports of azasteroid syntheses. One reported anomalous reaction in azasteroid synthesis involved the attempted cyclization of 51 with phosphorus oxychloride. The product, isolated in low yield, was 52, presumably formed through an intermediate of type 53. The same product could be isolated in good yield if the cyclization was carried out in polyphosphoric acid.

It was expected that cyclization of 54b in polyphosphoric acid should yield the azasteroid 55b. Heating 54b in polyphosphoric acid
on a steam bath for 6 hours, followed by an aqueous work-up and precipitation of the product with 10% aqueous perchloric acid, afforded a quantitative yield based on the molecular weight of the expected product. The pmr (Appendix B, Figure 6) indicated, however, that the product was actually a mixture composed of two compounds. Analysis of the aromatic region of the spectrum showed four overlapping singlets of approximately equal intensity between δ 7.0 and δ 8.0 and an AB quartet at approximately δ 9.0. In all precursors the two methoxyl peaks appear as a singlet, however the crude product showed two distinctly separated methoxyl absorbances of approximately equal intensity. The infrared spectrum of the material showed absorbances characteristic of hydroxyl, a conjugated ketone and several absorbances between 1500 and 1600 cm⁻¹.

The material was dissolved in acetonitrile and absolute ethanol added while the acetonitrile-ethanol azeotrope was removed. On standing a yellow solid crystallized from the solution, accounting for approximately half of the original material. Evaporation of the ethanol gave the remainder of the material as a golden oil which could be crystallized with difficulty.

Analysis of the first fraction indicated that it possessed structure $56b$. The aromatic pattern in the pmr indicated that it had cyclized to give the 2,3-dimethoxyl compound and not the 3,4-dimethoxyl isomer. The other aromatic absorptions were at a chemical shift characteristic of the ring protons of a pyridinium salt (δ 9.0) and appeared as a closely spaced AB pattern ($J=9.0$ Hz) in dimethylsulfoxide and a more separated AB pattern in trifluoroacetic acid. The remainder of the spectrum consisted of an $A_2B_2$ pattern characteristic of that found
in the precursors for the methylene protons of the five membered ring and an $A_2B_2$ pattern for the methylene protons of the phenethylamine moiety. The infrared spectrum showed an absorption at 1720 cm$^{-1}$ for the 17-carbonyl.

The second fraction was identified as compound 57b, based on spectral and chemical evidence. Analysis of the pmr spectrum (Appendix B, Figure 10) indicated that, as with 56b, cyclization had given the 2,3-dimethoxyl compound. The lack of absorbances characteristic of vinyl protons limited any unsaturation outside the A-ring to the 8(9)-, 8(14)-, 13(14)- or 13(17)- positions assuming a substituent at the 17-position. An ill-defined quartet at $\delta$ 4.76 was in good agreement with the C-9 proton in other A-ring aromatic 8-azasteroids. This restricts all multiple bonds to the 8,14,13,17-system.

The infrared spectrum showed a hydroxyl stretching absorption at approximately 3300 cm$^{-1}$ as well as absorptions at 1610 and 1500 cm$^{-1}$. The carbonyls in enaminoketones appear at approximately this wavelength but protonation of nitrogen would be expected to cause a shift of the ketone absorption to higher wavelength. As there is either an N-H or O-H, the lack of a higher wavelength absorption for the carbonyl group was considered presumptive evidence against N-protonation. Since the compound is a salt and lacks N-H, a double bond must be present at 8(14)-.

Treatment of 57b with aqueous base and methylene chloride, separation and drying of the organic layer, and subsequent evaporation of the methylene chloride yielded a golden oil that darkened with time on contact with air. This compound could be crystallized from ethyl acetate-hexane and in the crystalline form the compound was relatively stable. This compound (58b) lacked an N-H or O-H as determined by the
infrared spectrum but the spectrum did show the absorption bands at approximately 1640 cm\(^{-1}\) characteristic of an enaminoketone.

The addition of aqueous perchloric acid to 58b regenerated 57b which precipitated as the monohydrate and could be recrystallized as the anhydrous salt, the latter identical in all respects with the original material (57b). The treatment of 57b with base and its subsequent regeneration on addition of acid are consistent with the assigned structure of an O-protonated enaminoketone for 57b.

O-Protonated enaminoketones are not without precedence in the literature. Examples of enaminoketones, both cisoid and transoid, have been reported in azasteroids and all of these give O-protonation.\(^9,10,52\) The azasteroids 60 and 61, with aqueous perchloric acid, gave the

\[
\begin{align*}
\text{60} \\
\text{61} \\
\text{62} \\
\text{63}
\end{align*}
\]
O-protonated salts 62 and 63 respectively.\textsuperscript{10,53} Compound 62 was reported to give an infrared spectrum with absorptions at 3110 and 1640 cm\textsuperscript{-1} and 63 at 3115 and 1642 cm\textsuperscript{-1}. Azasteroids 64 and 65 provided an enaminoketone system more closely related to that of 57b and 58b.\textsuperscript{52}

![Chemical structures of 64 and 65](image)

The spectral characteristics of these two compounds differ very little and their agreement with the data for compounds 57b and 58b (see Table I) is reasonable. Differences between these two systems can be explained in terms of the differences in strain between the 5- and 6-membered rings.

Table I. Comparison of Spectral Data for 57b, 58b, 64 and 65.

<table>
<thead>
<tr>
<th></th>
<th>Salts</th>
<th>Free Bases</th>
</tr>
</thead>
<tbody>
<tr>
<td>57b</td>
<td>64</td>
<td>58b</td>
</tr>
<tr>
<td>IR (cm\textsuperscript{-1})</td>
<td>1610\textsuperscript{a}</td>
<td>1620\textsuperscript{b}</td>
</tr>
<tr>
<td>UV\textsuperscript{d}</td>
<td>293.5(4.6)</td>
<td>318(4.5)</td>
</tr>
<tr>
<td>par (C-9)</td>
<td>6 4.76\textsuperscript{a}</td>
<td>-----\textsuperscript{f}</td>
</tr>
</tbody>
</table>

a-KBr; b-Nujol; c-CHCl\textsubscript{3}; d-EtOH; e-DMSO-d\textsubscript{6}; f-data not given; g-CDCl\textsubscript{3}
In order to determine if the reaction parameters have any effect on the ratio of products, several cyclizations were run in which the reaction time was varied. These results are summarized in Table II. In all cases the ratio of products was determined from the pnr spectrum of the crude product (e.g. Appendix B, Figure 6) by integration of the 1- and 4-aromatic protons of 56b and 57b. Yields were determined from the weight of the dried crude material. It appeared that the ratio of products remained constant regardless of whether or not the reaction had gone to completion and that the product ratio was approximately 1:1.

<table>
<thead>
<tr>
<th>Reaction Time</th>
<th>Total Yield</th>
<th>% 56b</th>
<th>% 57b</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 hr.</td>
<td>84%</td>
<td>55.0</td>
<td>45.0</td>
</tr>
<tr>
<td>6 hr.</td>
<td>100%</td>
<td>58.5</td>
<td>41.5</td>
</tr>
<tr>
<td>6 hr.*</td>
<td>92.5%</td>
<td>45.0</td>
<td>55.0</td>
</tr>
<tr>
<td>12 hr.</td>
<td>100%</td>
<td>55.5</td>
<td>44.5</td>
</tr>
</tbody>
</table>

* The polyphosphoric acid was heated to 90° prior to adding 54b. In all other runs, 54b was added to cold polyphosphoric acid and then heated.

It was anticipated that the monomethoxyl compound (54a) might be more difficult to cyclize than the corresponding dimethoxyl compound (54b) because of the decreased nucleophilicity of the aromatic ring. However, cyclization of 54a in polyphosphoric acid on a steam bath gave a quantitative yield (based on the molecular weight of the expected
perchlorate) in 8 hours. Analysis of the pmr spectrum of the crude product (Appendix B, Figure 5) showed the mixture to be composed of a 47:53 ratio of 56a and 57a respectively. The two compounds were separated by fractional crystallization in the same manner as with the corresponding dimethoxyl compounds and the aromatic patterns in the pmr confirmed the direction of cyclization as para to the methoxyl in both cases.

The treatment of 57a with base gave 58a as a solid which decomposed on standing. This compound exhibited spectral properties consistent with the assigned structure (58a). Several attempts to secure elemental analysis of 58a led to values outside the desired limits, however, mass spectral analysis gave a M+ molecular ion peak at 269 and a fragmentation pattern similar to that found for 58b (Appendix B, Figures 1 and 2).

The ratio of products as approximately 1:1 (within the limits of pmr analysis) for both the monomethoxyl and dimethoxyl series cannot be taken as coincidence. It would appear that the same mechanism was operative in both cases, possibly a disproportionation of the expected dihydropyridinium salt 55 or some similar compound (59).

The disproportionation of azasteroids is not without precedence in the literature. In 1968 Huisman and coworkers reported the synthesis of some 6-azasteroids. The cyclization of 66 with p-toluene sulfonic acid gave not the expected product, but 67, the formation of which is rationalized in terms of successive cyclization and disproportionation steps. The azasteroid 68, on treatment with a palladium catalyst, gave 69 and 70 in yields of 8% and 59% respectively.

Under certain conditions, the cyclization of 71 could yield 72,
presumably as a disproportionation product.\textsuperscript{16}

In the cyclization of 73, Meyers and coworkers reported the formation of a small amount of the pyridone 74 in addition to the expected dihydropyridone.\textsuperscript{7} The formation of 74 was explained, not as disproportionation, but as an oxidation of the dihydropyridone, the driving force being aromatization.

In the polyphosphoric acid cyclodehydration of 75 to form dihydrolepidine, the products isolated were lepidine (76) and tetrahydrolepidine (77) in a 1:1 ratio and in 90% yield.\textsuperscript{54} The authors ascribe this to an intermolecular hydride transfer of the dihydrolepidine, formed as the initial product of cyclization.
E. Reactions of the Azasteroids 56b, 57b and 58b.

The reactivity of the azasteroids 56b, 57b and 58b was investigated in the hope of providing 8-azasteroids similar to carbocyclic steroids known to possess pharmacological activity or possessing features similar to active carbocyclic steroids.

Apart from treatment with base to give 58b, the azasteroid 57b proved unreactive. All attempts to reduce the 8(14)-double bond to give 2,3-dimethoxy-1,3,5(10)-triene-8-aza-gonan-17-one (80) were unsuccessful. Addition of an excess of sodium borohydride to an ethanolic solution of the azasteroid 57b followed by an aqueous basic work-up after 30 minutes gave a good yield of 58b indicating that reduction had not occurred. Similarly, attempted hydrogenation of 57b over Adams Catalyst also gave only 58b after work-up.

![Chemical Structures](image)

It is possible that under the conditions of the two preceding reductions, deprotonation of the azasteroid occurred to give the enamino-ketone as the free base which would be inert to the reaction conditions. To test this hypothesis the azasteroid 57b was dissolved in ethanol saturated with hydrogen chloride. Attempted reduction over Adams
Catalyst followed by an aqueous work-up also afforded the azasteroid 58b in good yield.

It is reported that the azasteroid 78 will add methyl magnesium iodide in hexane to the iminium bond to give compound 79. To a suspension of finely powdered 57b in hexane was added an etherial solution of methyl magnesium iodide. Work-up of the reaction yielded a small amount of a dark oil, the infrared spectrum of which was identical to the enamino ketone 58b. There was no indication of an unconjugated carbonyl.
Unlike their O-protonated salts, the reduction of enamino-ketones is known to proceed fairly readily. In steroidal enamino-ketones, both cisoid and transoid, the reduction with lithium aluminum hydride gives the amino ketones. The reduction of the azasteroid with lithium aluminum hydride in dry tetrahydrofuran, followed by a basic work-up to give the more thermodynamically stable isomer, gave a moderate yield of a white solid. The material was shown to be homogeneous by thin layer chromatography. The compound exhibited an unconjugated carbonyl in the infrared at 1740 cm\(^{-1}\) and had absorbances at 2810 and 2890 cm\(^{-1}\) (Bohlmann bands). The ultraviolet spectrum showed no chromophores other than the carbonyl and the aromatic ring (281 nm, \(\log\varepsilon = 3.8\)). The Bohlmann bands indicated a trans-anti geometry for the 9,8,14-system.

Four isomeric 8-azasteroids have been prepared by other workers and their stereochemical assignments have been made by X-ray crystallography. Of these isomers, only the trans-anti-cis and the trans-anti-trans show Bohlmann bands, as expected. The methylene envelopes of these two isomers are unique and comparison of the pmr spectra of these isomers to that obtained for compound unequivocally determined the stereochemistry as the trans-anti-cis isomer. This isomer is the most stable of those expected from the reduction and presumably arose from a base catalyzed equilibration which occurred in the reaction work-up.

In an attempt to introduce a substituent onto the 13-carbon, the azasteroid was heated under reflux with methyl iodide. The only product isolated was the C-methyl salt in 90% yield. Meyers and coworkers studied the alkylation of cisoid and transoid enamino-ketones.
with alkyl halides and found that aprotic solvents produced a mixture of O- and C-alkylated products in cisoid enaminoketones while protic solvents gave only O-alkylation and O-protonation. All transoid enaminoketones studied gave only O-alkylation, although no system was reported in which the ketone was in a five membered ring and no alkylation of a transoid enaminoketone in an azasteroid was reported. The attempted alkylation of 58b with methyl iodide in acetonitrile, conditions which Meyers found to give predominately C-alkylation with cisoid enaminoketones, afforded only ill-defined, hygroscopic products.

The O-methyl enaminoketone salt 81 had an infrared spectrum almost identical to that of the O-protonated azasteroid 57b, the only differences being the lack of absorptions due to the hydroxyl and perchlorate and small changes due to absorption bands due to the additional methoxyl. With the exception of the deletion of the hydroxyl resonance band and the addition of a methoxyl resonance absorption, the pmr spectrum of 81 is very similar to that of 57b, the only other differences being subtle changes in the methylene envelope. The ultraviolet spectra are also quite similar, having maxima at 293.5 nm ($\log \varepsilon = 4.6$) for 57b and 290 nm ($\log \varepsilon = 4.6$) for 81.
The similarity between the ultraviolet spectra of a transoid enaminoketone, its O-protonated salt and a similar O-alkylated enaminoketone has been noted by other workers. The azasteroid should not undergo facile demethylation and, if would not reduce because of its ready deprotonation, the immonium bond in compound should be readily reducible. Reduction of was initially attempted in ethanol with palladium on carbon at room temperature and one atmosphere of hydrogen pressure. After 3 hr no reduction had occurred based on the failure of the ultraviolet absorption to change. The reduction of with a two fold excess of sodium borohydride in ethanol gave an immediate change in the ultraviolet spectrum, and the reaction was complete within 15 minutes (no further change in the spectrum being noted). The product was separated into two fractions by chromatography on neutral alumina.

The first fraction gave spectral data completely inconsistent with the desired product. Most obvious was the lack of the 17-methoxyl signal in the pmr spectrum and the appearance of a broad singlet in the vinyl proton region. Irradiation of this signal gave no noticeable change in the methylene region of the spectrum but by random irradiation of the methylene region it was possible to sharpen the vinyl absorption into a sharp singlet. The infrared spectrum showed weak absorbances at 1675 and 1630 cm\(^{-1}\) in addition to those for the aromatic ring. There were also strong absorbances at 2910 and 2810 cm\(^{-1}\) (Bohmann bands). The ultraviolet spectrum showed absorption characteristic of the di-methoxy benzene ring (282 nm, \(\log \varepsilon = 3.6\); 286 nm \(\log \varepsilon = 3.6\)), indicating that there is no chromophore conjugated with the aromatic ring.

From the appearance of the one vinyl absorption it is clear that compound must possess the structure indicated, the stereochemistry
of the 9,8,14-system determined as trans-anti by the presence of strong Bohlmann bands.

The second fraction (82) lacked the vinyl absorption in the pmr spectrum which characterized the azasteroid 82, and the spectrum showed absorption bands due to three methoxyl groups. The ultraviolet absorption spectrum was identical with that obtained for 82 (282 nm, log ε =3.6; 286 nm, log ε =3.6). The infrared spectrum showed strong absorptions at 2800 and 2900 cm⁻¹ (Bohlmann bands) and additional absorptions for the methoxyl in the region of 1000 to 1100 cm⁻¹. A strong band at 1690 cm⁻¹ was assigned as a stretching vibration of a strained unconjugated enol ether. The spectral characteristics and the elemental analyses led to the assignment of the structure as 83.

The appearance of the unexpected product (82) from the reduction can be rationalized as a nucleophilic substitution reaction. This could occur by either of two mechanisms, both of which involve the novel 1,4-addition of hydride to the O-methyl enamino ketone salt (attack at b in Scheme 7). This may be followed either by displacement of the methoxyl by the electron pair on the nitrogen (c in Scheme 7) followed
Scheme 7
by a 1,2-reduction of the resulting immonium system (e in Scheme 7)
or by a displacement of the allylic methoxyl by hydride (d in Scheme
7). The azasteroid 83 arises from a simple reduction of the immonium
bond (hydride attack at a in Scheme 7).

Alkyl substituents have been introduced by means of a Claisen
type rearrangement of O-allyl enol ethers. The azasteroid 58b
proved more resistant to alkylation with allyl bromide than with
methyl iodide in spite of the reactivity of allyl bromide. When heated
under reflux neat with allyl bromide, under a nitrogen atmosphere for
a week, the only product isolated was the bromide salt of the O-proton-
ated enaminoketone. Heating under reflux for 24 hr in dry acetone with
an excess allyl bromide afforded the O-allyl salt (84) in moderate yield.
No trace of the C-alkylated product was found.

The infrared and ultraviolet spectral data of this compound
were very similar to that obtained for the O-methyl salt, with additional
absorptions in the infrared spectrum for the isolated double bond of
the allyl group.

Rearrangement of the azasteroid 84 was attempted by heating a
finely powdered sample of the salt in refluxing toluene for 19 hr.
At the end of the reaction period all material had gone into solution.
The solvent was removed under reduced pressure to give an oil. The
infrared spectrum of this oil was identical with that of the steroidal
enaminoketone 58b. This product could arise from the elimination of
allyl bromide in preference to rearrangement of the salt. This is
undoubtedly due in large measure to the nucleophilicity of the bromide.
Replacement of the bromide with a less nucleophilic anion may result
in rearrangement being favored over elimination.
Attempts were made to prepare the O-allyl tosylate salt of the enaminoketone $58b$. The reaction of $58b$ with allyl tosylate in either dry acetone or dry tetrahydrofuran gave a red viscous oil from which no product could be isolated. In its preparation allyl tosylate was shown to be extremely prone to decomposition and polymerization.

Pyridinium salts can be reduced under a variety of conditions to yield either partially or fully reduced pyridine derivatives. There are several examples of catalytic hydrogenation of pyridinium salts containing an electron withdrawing substituent in the 3-position being reduced to the 1,4,5,6-tetrahydro-pyridine derivative. The azasteroid $56b$ proved too insoluble for catalytic reduction. The reduction was attempted by combining the azasteroid, ethanol and Adams Catalyst in a Paar bottle and shaking at a hydrogen pressure of 50 psi for one week. Filtration of the reaction mixture afforded starting material in almost quantitative yield and evaporation of the ethanol gave traces of a material which was not investigated further.

The addition of an excess of sodium borohydride dissolved in water to a solution of $56b$ in acetonitrile gave an immediate color
change from yellow to purple and on stirring the solution all material dissolved within five minutes. Aqueous acid was added to decompose the excess sodium borohydride and any amine borane which might have been formed. The solution was made basic and extracted with methylene chloride to give a low yield of the steroidal enaminoketone 56b, identical in all respects with an authentic sample.

This material may arise from two sources. The first is the direct reduction of 56b. The second possible source involves an initial reduction of 56b to give a dihydropyridine (85). This material may disproportionate to give the two azasteroids 57b and 56b in a manner similar to that in the cyclization of the dihydropyridone 50.

Modifications of the azasteroid which would result in the introduction of an aminomethyl moiety at the 12-position were sought. The proposed method for its introduction involved a nucleophilic attack by cyanide ion on the 12-position of the azasteroid 56b to give 86. The reduction of the 9(11)-double bond would then give the target compound 87.

The addition of cyanide ion to pyridinium salts possessing
electron withdrawing substituents at the 3- and/or 5-positions to
give 4-cyano-1,4-dihydropyridine derivatives is well known. Additions
of this type are generally carried out in water and result in the
immediate formation of the cyano adduct as a yellow precipitate.

The low solubility of 56b in water complicated any attempt to
add cyanide. If an aqueous solution of potassium cyanide was added
to a rapidly stirred suspension of the azasteroid 56b in water, an
immediate color change to a deep purple was observed. The colored
material was extractable into chloroform and evaporation of the chloro-
form yielded a black material (88) which exhibited no absorptions in
the infrared spectrum characteristic of a nitrile. The material had
no definable melting point and could not be recrystallized. A similar
material was prepared from the addition of cyanide to 56b in acetonitrile.
The solid state ESR spectrum exhibited a signal at a field characteristic
of an organic free radical. The strength of the signal indicated only
a small percentage of the material was in the radical form. A solution
spectrum in chloroform (10⁻³ molar based on a molecular weight of 400)
gave some hint of fine structure in the bands but also showed only a
small fraction of the compound to be radical in nature.

To a 10^{-3} molar degassed solution of 56b in acetonitrile was added anhydrous potassium cyanide. An immediate color change to a purple was evident. It was hoped that by using a freshly prepared and degassed solution that a higher radical concentration could be obtained and the appearance of fine structure in the ESR spectrum would result. The ESR spectrum showed almost no radical formation. The original material was prepared in acetonitrile at a concentration of 10 mg/ml and concentrated to collect the product. A solution exhibiting no ESR signal was prepared at a concentration of 1.5 mg/ml.

Winters and coworkers have reported the preparation of a viologen radical cation (89) from the reaction of N-alkyl pyridinium salts with cyanide ion. The reaction of N-benzyl pyridinium salts with cyanide ion gave a material composed of 10-20\% radical cation (based on estimates from the ESR spectrum), the remainder of the material being 90.
Figure 1. Addition of Cyanide Ion to 56b.
The azasteroid 56b exhibited absorption maxima in the ultraviolet region in acetonitrile at 407, 336, 295, 280 and 235 nm (Figure 1, curve a). The addition of anhydrous potassium cyanide to the ultraviolet cell gave the spectral changes indicated, the loss of 407, 336, 295 and 280 nm maxima and appearance of a large absorption at 268 nm. The product of the addition of cyanide ion to 56b in acetonitrile at a concentration of 10 mg/ml (98) exhibited a maxima at 270 nm and several other absorbances (Figure 1, curve e), but the spectrum was not identical to that obtained from the reaction run at dilute concentration (uv scale).

Based on the ultraviolet and ESR spectral work it appeared that there were competitive reactions. One, predominating in dilute solutions, was the addition of cyanide ion to the 12-position of 56b to give the desired adduct 86 (Figure 1, a-d). A second reaction, predominating in more concentrated solutions or after standing in dilute solution, was the formation of the radical cation 91 and the Z and E mixture of 92.
The presence of $^{22}$ could account for the lack of fine structure in the ESR spectrum of $^{21}$ due to electron transfer between $^{21}$ and $^{22}$.

In order to synthesize $^{87}$, attempts were made to add cyanide ion to $^{56b}$ in dilute solutions (approximately 1 mg/ml) and reduce the 9(11)-double bond without isolating $^{86}$. All attempts listed in Table III were unsuccessful and no isolated materials, except where specified, contained either a ketone, conjugated or unconjugated, an enaminoketone, or a nitrile, as determined by infrared. In those cases where $^{58b}$ was isolated, it may result from the reduction of $^{56b}$ which has not added cyanide, from a reversible cyanide adduct of $^{56b}$ or from reductive decyanolation.

The synthesis of the 8-azasteroids $^{56}$ and $^{57}$ provided compounds which have the potential for modification to azasteroids of potential clinical importance. These compounds have been sent to the Drug Development Branch, National Institutes of Health, for screening as potential antineoplastic agents. The lack of basicity of the nitrogen in the azasteroid $^{56}$ may enhance its desirability as an antifertility agent. Although cyanide ion addition to the azasteroid $^{56}$ was not accomplished, it is hoped that a less basic source of cyanide ion such as diethyl aluminum cyanide may be effective in causing this transformation.
Table III. Addition of Cyanide Ion to $56b$.

<table>
<thead>
<tr>
<th>Solvent(s) for Cyanide Addition</th>
<th>Reduction Conditions</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetonitrile 5 mg/ml</td>
<td>Sodium Borohydride/water/acetonitrile/1 hr.</td>
<td>$56b$</td>
</tr>
<tr>
<td>Methylene Chloride 20 mg/ml</td>
<td>Sodium Borohydride/95% ethanol/1 hr.</td>
<td>$56b$</td>
</tr>
<tr>
<td>Acetonitrile (degassed) 1 mg/ml</td>
<td>Sodium Borohydride/water/acetonitrile/1 hr.</td>
<td>?</td>
</tr>
<tr>
<td>Acetonitrile 1 mg/ml</td>
<td>Sodium Borohydride/water/acetonitrile/1 hr.</td>
<td>?</td>
</tr>
<tr>
<td>Acetonitrile 1.25 mg/ml</td>
<td>Sodium Borohydride/water/acetonitrile/overnight</td>
<td>?</td>
</tr>
<tr>
<td>95% Ethanol 1 mg/ml</td>
<td>PtO$_2$/H$_2$-50 psi/95% ethanol/22 hrs.</td>
<td>?</td>
</tr>
<tr>
<td>Ethanol(abs) 1 mg/ml</td>
<td>Sodium Borohydride/ethanol/acetic acid</td>
<td>?</td>
</tr>
<tr>
<td>Ethanol(abs) 1 mg/ml</td>
<td>10%Pd-C/H$_2$-50 psi/ethanol/48 hrs.</td>
<td>?</td>
</tr>
<tr>
<td>Methylene Chloride 1 mg/ml</td>
<td>Sodium Borohydride/methylene chloride/acetic acid</td>
<td>?</td>
</tr>
<tr>
<td>Acetic acid</td>
<td>Acetic acid/10% Pd-C/H$_2$-50 psi/22 hrs.</td>
<td>?</td>
</tr>
<tr>
<td>Dimethylsulfoxide 2.5 mg/ml</td>
<td>Sodium Borohydride/dimethylsulfoxide/acetic acid/3 hrs.</td>
<td>$56b$</td>
</tr>
</tbody>
</table>

* The ratio of potassium cyanide to $56b$ was 1:1 by weight.
F. Synthesis of the Enaminoketone and Dihydropyridone with 1,3-cyclo-
hexadione.

In an attempt to synthesize a series of D-homo-8-azasteroids, reactions analogous to those carried out with 1,3-cyclopentadione were run with 1,3-cyclohexadione. The reaction of 1,3-cyclohexadione with β-3,4-dimethoxyphenethylamine gave the enaminoketone 93 in quantitative yield. This compound gave spectral data similar to that obtained for the analogous compound synthesized with the five membered ring (37b) except that the ultraviolet spectrum exhibited a maximum at 288 nm while the 5-membered enaminoketone had a maximum at 271 nm. This difference was attributable to the increase in strain of the double bond enolizing into the 5-membered ring over that in the 6-membered ring, shifting the absorption of 37b to higher energy.

The reaction of the enaminoketone 93 with β-propiolactone in chlorobenzene gave an excellent yield of the desired dihydropyridone 94. The dihydropyridone 94 had absorptions in the infrared region at
1675, 1625, 1600 and 1505 cm⁻¹ which were similar to those obtained for the dihydropyridone 50b fused to the 5-membered ring. The ultraviolet spectrum of 94 had maxima at 230 and 299 nm, exhibiting a red shift of 13 nm from the dihydropyridone 50b fused to the 5-membered ring.

An attempt was made to cyclize the dihydropyridone 94 under conditions identical to those used in the cyclization of the dihydropyridones 50. The product which was isolated did not consist of a mixture of two compounds but appeared to be the salt of a single compound. Treatment of this salt with base did not give any material extractable into organic solvents. The infrared spectrum of this salt showed absorptions characteristic of a hydroxyl group. No further work was done on the determination of the structure of this reaction product.
G. Synthesis of the Pyridones 25 and 96 from the Dihydropyridones 50b and 94 and their Reactivity.

In an attempt to find a compound which could be cyclized to an 8-azasteroid without the disproportionation which necessitated separation of compounds, the conversion of dihydropyridones to pyridones was attempted by other methods. The cyclization of these compounds should then give 8-azasteroids of the type 56.

Activated manganese dioxide is a reagent known to affect the dehydrogenation and aromatization of organic compounds. Manganese dioxide, prepared by the method of Attenburrow et al., was added to a solution of the dihydropyridone 50b in methylene chloride and the resulting slurry was stirred for 5 hr. Separation of the methylene chloride solution by filtration gave the desired pyridone 25 in moderate yield. Repeated washing of the filter cake failed to find either more of the pyridone or the remaining dihydropyridone. The remaining material may be bound to the solid material as a manganate ester. The identification of the material as the pyridone 25 was made on the basis of spectral data and elemental analysis. The pmr spectrum showed the AB pattern for the 3- and 4-protons in the aromatic region.

The dihydropyridone 94 was stirred with activated manganese dioxide under conditions identical to those used with 50b and afforded a moderate yield of the pyridone 96. Spectral data for this compound were very similar to those obtained for the pyridone 25. The ultraviolet spectra of the 5- and 6-membered series showed a red shift of 9 nm in going from the 5- to the 6-membered series.

Cyclization of both of these compounds was attempted under conditions identical to those used in the cyclization of the dihydro-
pyridones. In both cases no products other than the starting pyridones were isolated. In an attempt to affect cyclization the pyridones were heated to 150° in polyphosphoric acid. Under these conditions only tars were isolated.

\[ \text{CH}_3\text{O} \]
\[ \text{CH}_3\text{O} \]

\[ \text{Cl} \]
\[ \text{ClO}_4^- \]

The pyridone 96 was heated under reflux in phosphorus oxychloride in order to affect cyclization. This reagent has been used extensively in Bischler-Napieralski cyclizations and has been used in the synthesis of 8-azasteroids. The product, precipitated with aqueous perchloric acid, was found to be the uncyclized compound 97. This compound was readily characterized by elemental analysis and spectral data.

From this work it is evident that the route to the 8-azasteroids through the pyridones 95 and 96 is not as advantageous as is the route through the dihydropyridones 50.
SECTION III

EXPERIMENTAL

General

Melting Points. Melting points were determined with a Thomas Hoover Capillary Melting Point Apparatus or a Laboratory Devices Mel-Temp Melting Point Apparatus and are uncorrected.

Elemental Analyses. Elemental analyses were determined at the University of New Hampshire with an F & M Model 185 carbon, hydrogen and nitrogen analyzer.

Infrared Spectra. Infrared spectra were recorded on either a Perkin-Elmer Model 137 prism infrared spectrometer or a Perkin-Elmer Model 337 grating infrared spectrometer and were calibrated with polystyrene at 1601.4 or 906.7 cm\(^{-1}\). Solid samples were recorded as KBr discs while noncrystalline samples were recorded as neat films between sodium chloride plates.

Ultraviolet Spectra. Ultraviolet spectra were recorded on a Cary Model 15 spectrometer. The data are given in the experimental section as follows: uv \(\lambda_{\text{max}}^\text{solvent}\), wavelength in nm (log \(\varepsilon\)).

Nuclear Magnetic Resonance Spectra. All nuclear magnetic resonance spectra (designated pmr) were recorded on a Japan Electron Optics Laboratory Co., Ltd. Model MH-100 spectrometer and are reported in parts per million (\(\delta\)) from TMS. Samples recorded in CDCl\(_3\) contain 1% TMS as an internal standard, and samples recorded in DMSO-d\(_6\) are calibrated with DMSO, taken as 2.50 ppm downfield from TMS, as an internal standard. For all compounds reported, the pmr spectra are reproduced in Appendix 3 and given in the experimental section as follows.
δ in ppm (multiplicity, number of hydrogens, coupling constant in Hz). The description of multiplicity is s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.

Mass Spectra. Mass spectra were determined at the National Institutes of Health, Bethesda, Md. through the courtesy of Dr. Henry Fales.

Materials and Methods. A. Reagents: β-Propiolactone, 2,3,4-dimethoxyphenethylamine, polyphosphoric acid, methyl iodide and allyl bromide were purchased from Aldrich Chemical Company. Sodium Borohydride and lithium aluminum hydride were purchased from Alfa Inorganics.

B. Solvents: The following solvents were used without additional purification: isopropyl alcohol, chlorobenzene, chloroform, ethanol, drum ether, ethyl acetate, hexane, methanol, methylene chloride and petroleum ether (bp 30-60°). Benzene, anhydrous ether and toluene were stored over sodium wire while xylene was redistilled. Acetone was stored over 4-A molecular sieves. Tetrahydrofuran was distilled from lithium aluminum hydride and stored over 4-A molecular sieves.

C. Products: Unless otherwise indicated, the yields of the products are reported as the crude products which normally were of sufficient purity to be used in the following synthetic step without additional purification. Unless otherwise indicated, infrared and pmr spectra were recorded from analytically pure samples.

D. Experimental Methods: Reagents were weighed to the number of significant figures shown and then the figures were converted to moles (mol) or millimoles (mmol). After extraction, the extract was dried with the drying agent specified for at least one hour. The
extract was then filtered with suction and the filtrate was concentrated on a rotary evaporator.
Preparation of N-(β-3-methoxyphenethyl)-3-amino-cyclopent-2-ene-1-one (37a). To a one neck, 100 ml round bottom flask, equipped with a Dean-Stark trap and a condenser, was added 3.0 g (19.8 mmol) of β-3-methoxyphenethylamine, 1.94 g (19.8 mmol) of 1,3-cyclopentadione and 50 ml dry benzene. The suspension was stirred magnetically and heated under reflux until the theoretical amount of water was collected (ca. 2 hr). The solvent was removed under reduced pressure and the resulting solid was triturated with anhydrous ether. Filtration gave 4.5 g (98.5%) of N-(β-3-methoxyphenethyl)-3-amino-cyclopent-2-ene-1-one (37a): mp 104-6°C; pmr (CDCl₃) (Appendix B, Figure 1): δ 7.27 (m, 1H), δ 7.13 (m, 1H), δ 6.9-6.65 (m, 3H), δ 4.98 (s, 1H), δ 3.75 (s, 3H), δ 3.65-3.2 (m, 2H), δ 2.87 (t, 3H, J=6.5 Hz), δ 2.7-2.1 (m, 4H); ir (KBr) (Appendix A, Figure 1): 3190, 1630, 1570, 1540 cm⁻¹; uλmax° EtOH 271 nm (4.498).

Anal. Calcd for C₁₅H₁₇NO₂: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.91; H, 7.42; N, 5.98.

Preparation of N-(β-3,4-dimethoxyphenethyl)-3-amino-cyclopent-2-ene-1-one (37b). To a one neck, 500 ml round bottom flask, equipped with a Dean-Stark trap and a condenser, was added 10.0 g (55.3 mmol) of β-3,4-dimethoxyphenethylamine, 5.0 g (51.0 mmol) of 1,3-cyclopentadione and 250 ml of dry benzene. The suspension was stirred magnetically and heated under reflux until the theoretical amount of water was collected (ca. 2-3 hr). At this time the reaction was homogeneous. The solvent was removed under reduced pressure and the resulting solid triturated with anhydrous ether to give, on filtration, 13.1 g (98.3%) of N-(β-3,4-dimethoxyphenethyl)-3-amino-cyclopent-2-ene-1-one (37b) as an off white solid: mp 125-8°C; pmr (CDCl₃) (Appendix B, Figure 2):
$\delta$ 6.61 (broad, 1H), $\delta$ 6.58 (s, 3H), $\delta$ 4.87 (s, 1H), $\delta$ 3.73 (s, 6H);

ir (KBr) (Appendix A, Figure 2): 1510, 1540, 1560, 3180 cm$^{-1}$; uv $\lambda_{\text{max}}$ EtOH: 229 nm (3.96), 271 nm (4.56).

Anal. Calcd for C$_{15}$H$_{15}$NO$_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.82; H, 7.20; N, 5.19.

Preparation of N-(B-3-methoxyphenethyl)-1,2,3,4-tetrahydro-pyridan-2,5-dione (50a). To a 250 ml, one neck round bottom flask, was added 4.0 g (17.35 mmol) of N-(B-3-methoxyphenethyl)-3-amino-cyclopent-2-ene-1-one (37a), 4.0 g (55.5 mmol) of B-propiolactone and 125 ml chlorobenzene. The solution was heated under reflux for three days. The condenser was removed, the flask was fitted with a distillation head and condenser, and 20 ml of chlorobenzene-water azoetrop was removed by distillation. The distillation head was removed, 20 ml of dry chlorobenzene were added to the flask, the condenser was replaced, and reflux was continued for an additional five days. The solvent was evaporated under reduced pressure and the residue was dissolved in 20 ml ethyl acetate. The solution was passed over a column of neutral alumina and eluted with ethyl acetate. Evaporation of the solvent under reduced pressure gave a solid which was recrystallized from benzene/pentane to give 3.4 g (68.8%) of N-(B-3-methoxyphenethyl)-1,2,3,4-tetrahydro-pyridan-2,5-dione (50a); mp 119-20$^\circ$; pmr (CDCl$_3$) (Appendix B, Figure 3): $\delta$ 3.82 (t, 2H, J=7.0 Hz), $\delta$ 3.74 (s, 3H), $\delta$ 2.87 (t, 2H, J=7.0 Hz), $\delta$ 2.33 (s, 4H); ir (KBr) (Appendix A, Figure 3): 1400, 1620, 1670 cm$^{-1}$; uv $\lambda_{\text{max}}$ EtOH: 291 nm (4.23), 282 nm (4.21), 218 (4.09).

Anal. Calcd for C$_{17}$H$_{19}$NO$_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.67; H, 6.66; N, 4.82.
Preparation of N-(3-3.4-dimethoxyphenethyl)-1,2,3,4-tetrahydro-pyrindan-2,5-dione (50b). To a one neck, 5 l round bottom flask, equipped with a condenser, was added 100.0 g (0.38 mol) of N-(β-3,4-dimethoxyphenethyl)-3-amino-cyclopent-2-ene-1-one (32b), 150 g (2.08 mol) of β-propiolactone and 3 l of chlorobenzene. The solution was heated under reflux for seven days. Every 24 hours 200 ml of chlorobenzene was distilled off to remove any water formed from the reaction. The same amount of dry chlorobenzene was then added. The solvent was removed under reduced pressure and the resulting red oil was chromatographed on neutral alumina and eluted with ethyl acetate. Evaporation of the ethyl acetate under reduced pressure gave a solid which was recrystallized from isopropanol to give 81.5 g (67.5%) of N-(β-3,4-dimethoxyphenethyl)-1,2,3,4-tetrahydro-pyrindan-2,5-dione (50b); mp 156-8°; pmr (CDCl₃) (Appendix B, Figure 4): δ 6.74 (m, 3H), δ 3.88 (m, 8H); ir (KBr) (Appendix A, Figure 4): 1520, 1640, 1680 cm⁻¹; uv λ_max^EtOH: 228 nm (4.1), 286.5 nm (4.2).

Anal. Calcd for C₁₆H₂₁NO₄: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.64; H, 6.78; N, 4.43.

Alternatively the reaction could be run using a mixture of xylenes as the solvent. In this case the water was removed with a Dean-Stark trap, the reaction time was decreased to 20 hr, and a slightly larger excess of β-propiolactone was used (approximately 15%). Under these conditions the yields varied from 41-50%.

Cyclization of N-(β-3-methoxyphenethyl)-1,2,3,4-tetrahydro-pyrindan-2,5-dione (50a). A mixture of 10 g of polyphosphoric acid and 1.5 g (5.27 mmol) of N-(β-3-methoxyphenethyl)-1,2,3,4-tetrahydro-pyrindan-2,5-dione (50a) in a 50 ml beaker was heated on a steam bath.
for 8 hr. Ice (40g) was added and the reaction mixture was allowed
to stand, with occasional stirring, until the ice melted. Aqueous
perchloric acid (10%) was added dropwise with stirring until precipita-
tion ceased. The beaker was covered and cooled overnight at about 5°.
The precipitate was collected by filtration, washed with cold water, and
dried to a constant weight, yield 1.9 g (99%). The solid was dissolved
in 50 ml of acetonitrile. The solution was heated to boiling and
50 ml of absolute ethanol was added in portions. The volume was
reduced to 50 ml by boiling off the azeotrope and the solution was
cooled overnight at about 5°. The resulting solid was collected by
filtration and dried to give 0.78 g (41%) of 3-methoxy-1,3,5(10),8,11,13-
hexaene-8-aza-gonan-17-one perchlorate (56a): mp 263-4° d; pmr
(DMSO-d6) (Appendix B, Figure 7): δ 8.60 (AB, 2H), δ 8.32 (d, 1H, J=
8.5 Hz), δ 4.27 (t, 2H, J=6.5 Hz), δ 3.91 (s, 3H), δ 3.34 (t, 2H, J=
6.5 Hz); ir (KBr) (Appendix A, Figure 5): 1700, 1596, 1575, 1545 cm⁻¹;
uv λmaxEtOH: 286 nm (3.78), 265 nm (3.83).

Anal. Calcd for C17H16NO6Cl: C, 55.82; H, 4.41; N, 3.83.
Found: C, 55.65; H, 4.45; N, 4.10.

The solvent was evaporated from the filtrate and the residue was
recrystallized from acetone-petroleum ether to give 0.75 g (39%) of
3-methoxy-1,3,5(10),8(14),13(17)-pentaene-8-aza-gonan-17-ol perchlorate
(57a) as a yellow solid: mp 220-222°; pmr (TFA) (Appendix B, Figure
9): δ 7.12 (d, 1H, J=8.0 Hz), δ 4.70 (d, 1H, J=11.0 Hz), δ 3.76 (s, 3H); ir (KBr) (Appendix A, Figure 7): 1650, 1600, 1495, 1440, 1400,
1350 cm⁻¹; uv λmaxEtOH: 293 nm (4.52).

Anal. Calcd for C17H20NO6Cl: C, 55.22; H, 5.45; N, 3.79.
Found: C, 55.37; H, 5.46; N, 3.71.
Cyclization of N-(8-3,4-dimethoxyphenethyl)-1,2,3,4-tetrahydro-
pyridan-2,5-dione (50b). To 30 g of polyphosphoric acid at 90° in a
125 ml beaker was added 3.8 g (12.05 mmol) of N-(β-3,4-dimethoxyphen-
ethyl)-1,2,3,4-tetrahydro-pyridan-2,5-dione (50b). The solution was
heated six hours with occasional stirring. During the heating the
solution became bright red. The reaction was quenched with 90 g of
crushed ice and the beaker was set aside until the ice melted. At this
point the solution became yellow. Aqueous perchloric acid (10%) was
added dropwise with stirring until precipitation ceased. The beaker was
covered and cooled overnight at approximately 5°. The precipitate was
removed by filtration, washed with cold water and dried to a constant
weight to yield 4.42 g (92.5%). Subsequent runs ranged from 92-100%.
The solid was dissolved in 150 ml of boiling acetonitrile. To this
was added in portions 300 ml of absolute ethanol. The solution was
concentrated to 175 ml by evaporation and was allowed to cool. After
standing overnight at room temperature, the solution deposited crystals
which were collected by filtration and dried to give 2.0 g (42.2%) of
2,3-dimethoxy-1,3,5(10),8,11,13-hexaene-8-aza-gonan-17-one perchlorate
(56b); mp 294-5°; pmr (DMSO-d6) (Appendix B, Figure 8); δ 8.95,
8.86, 8.84, 8.76 (q, 2H), δ 7.95 (s, 1H), δ 7.42 (s, 1H), δ 4.86 (t,
2H, J=7.0 Hz), δ 3.74 (m, 2H), δ 3.43 (t, 2H, J=7.0 Hz), δ 3.10 (m, 2H);
ir (KBr) (Appendix A, Figure 6): 1720, 1605, 1595, 1550 cm⁻¹; uv λmax
337 nm (3.85), 299 nm (3.99), 281 nm (3.94), 236 nm (3.90).
Found: C, 54.42; H, 4.63; N, 3.56.
Evaporation of the filtrate gave 1.9 g (39.9%) of 2,3-dimethoxy-
1,3,5(10),8(14),13(17)-pentaene-8-aza-gonan-17-ol perchlorate (57b);
mp 208-9°C; pmr (DMSO-d$_6$) (Appendix B, Figure 10): $\delta$ 8.44 (s, 2H),
$\delta$ 6.96 (s, 1H), $\delta$ 6.82 (s, 1H), $\delta$ 4.76 (d, 1H, J=9.0 Hz), $\delta$ 3.74 (s, 6H);
ir (KBr) (Appendix A, Figure 8): 3300, 1610, 1500 cm$^{-1}$; uv $\lambda$$_{max}$: 293.5
nm (4.58).

Anal. Calcd for C$_{18}$H$_{22}$NOCl: C, 54.35; H, 5.07; N, 3.52.
Found: C, 54.22; H, 5.39; N, 3.47.

Preparation of 3-methoxy-1,3,5(10),13-tetraene-8-aza-gonan-
17-one (58a). To a stirred suspension of 0.50 g (1.34 mmol) of 3-methoxy-
1,3,5(10),8(14),13(17)-pentaene-8-aza-gonan-17-ol perchlorate (57a)
in 30 ml methylene chloride was added 10 ml of 5% aqueous sodium
hydroxide. The resulting reaction mixture was stirred under nitrogen
for 15 minutes. The layers were separated and the aqueous layer was
extracted with methylene chloride. The combined organic phases were
washed with water and dried over anhydrous magnesium sulfate. The
drying agent was removed by filtration and the solvent was evaporated.
The resulting oil was crystallized from acetone-hexane to give 0.30 g
(82.4%) of 3-methoxy-1,3,5(10),13-tetraene-8-aza-gonan-17-one (58a):
mp 122-5°C; pmr (CDCl$_3$) (Appendix B, Figure 11): $\delta$ 4.67 (m, 1H),
$\delta$ 3.90 (s, 1H); ir (neat) (Appendix A, Figure 9): 1670, 1600, 1565 cm$^{-1}$;
uv $\lambda$$_{max}$: 293 nm (4.5); mass spectrum (Appendix C, Figure 1, Table 1):
269 (M$^+$_).}

Anal. Calcd for C$_{17}$H$_{19}$NO$_2$: C, 75.81; H, 7.11; N, 5.20.
Found: C, 74.40; H, 7.19; N, 5.02.

Preparation of 2,3-dimethoxy-1,3,5(10),13-tetraene-8-aza-gonan-
17-one (58b). To a stirred suspension of 0.50 g (1.52 mmol) of 2,3-
dimethoxy-1,3,5(10),8(14),13(17)-pentaene-8-aza-gonan-17-ol perchlorate
(57b) in 25 ml methylene chloride was added 10 ml of 5% aqueous sodium
hydroxide. The reaction mixture was stirred under nitrogen for 15 minutes. The layers were separated and the aqueous phase was extracted twice with 10 ml portions of methylene chloride. The combined organic phases were washed with two 20 ml portions of water and then dried over magnesium sulfate under nitrogen. The drying agent was removed by filtration and the solvent was evaporated. The addition of ether to the residue gave a white solid which was recrystallized from ethyl acetate-hexane to give 0.24 g (64%) of 2,3-dimethoxy-1,3,5(10),13-tetraene-8-aza-gonan-17-one (58b); mp 158-60°; pmr (CDCl₃) (Appendix B, Figure 12): δ 6.80 (s, 1H), δ 6.68 (s, 1H), δ 4.52 (d, 1H, J=10.0 Hz); ir (KBr) (Appendix A, Figure 10): 1640, 1560, 1490 cm⁻¹; uv λmax: 293 nm (4.63), 228 nm (4.00); mass spectrum: (Appendix C, Figure 2, Table 2).

Anal. Calcd for C₁₈H₂₁NO₅: C, 72.22; H, 7.07; N, 4.68.
Found: C, 72.04; H, 7.00; N, 4.61.

Preparation of 2,3-dimethoxy-1,3,5(10),8(14),13(17)-pentaene-8-aza-gonan-17-ol perchlorate (57b). To a solution of 0.10 g (0.33 mmol) of 2,3-dimethoxy-1,3,5(10),13-tetraene-8-aza-gonan-17-one (58b) in 5 ml of 95% ethanol was added 10 drops of 10% aqueous perchloric acid. The solution was cooled overnight and the precipitate which formed was collected by filtration to give 0.10 g (75%) of 2,3-dimethoxy-1,3,5(10),8(14),13(17)-pentaene-8-aza-gonan-17-ol perchlorate (57b) as the monohydrate; mp 120-2°.

Found: C, 51.26; H, 5.80; N, 3.28.

The solid was dissolved in 20 ml acetonitrile and 40 ml absolute ethanol. The volume of the solution was reduced to 20 ml. Hexane
was added and the solution was cooled. The resulting solid, mp
208-9°, was collected by filtration. This material was identical
in all respects with the material from the cyclization of 50b.

Anal. Calcd for C₁₈H₂₂NO₇Cl: C, 54.35; H, 5.07; N, 3.52.
Found: C, 54.02; H, 5.70; N, 3.47.

Preparation of 2,3-dimethoxy-1,3,5(10)-triene-9β,13β,14β-8-
aza-gonan-17-one (80). To 1.0 g (3.3 mmol) of 2,3-dimethoxy-1,3,5(10),13-
tetraene-8-aza-gonan-17-one (58b) dissolved in 80 ml of dry tetrahydro-
furan was added 0.25 g lithium aluminum hydride. The resulting
solution was heated under reflux for 3 hr. Aqueous 10% sodium hydroxide
was added to decompose the excess lithium aluminum hydride, and the
resulting solid was removed by filtration. The solution was evaporated
under reduced pressure and the residue was recrystallized from hexane
to give 0.25 g (25%) of 2,3-dimethoxy-1,3,5(10)-triene-9β,13β,14β-8-
aza-gonan-17-one (80): mp 150-2°; pmr (CDCl₃) (Appendix B, Figure
13): δ 6.71 (s, 1H), δ 6.58 (s, 1H), δ 3.85 (s, 6H); ir (KBr).
(Appendix A, Figure 11): 2900, 2800, 1740, 1600, 1520 cm⁻¹; uv λ<sub>max</sub>:
281 nm (3.84).

Anal. Calcd for C₁₆H₂₃NO₃: C, 71.73; H, 7.69; N, 4.64.
Found: C, 71.65; H, 7.88; N, 4.44.

Preparation of 2,3,17-trimethoxy-1,3,5(10),8(14),13(17)-pentaene-
8-aza-gonane iodide (81). To a 25 ml round bottom flask equipped with
a condenser was added 103.6 mg (0.346 mmol) of 2,3-dimethoxy-1,3,5(10),13-
tetraene-8-aza-gonan-17-one (58b) and 5 ml methyl iodide. The
reactants were heated under reflux under a positive pressure of nitrogen
for 17 hrs. The solid which formed was collected by filtration and
washed with dry ether. Recrystallization of the solid from methanol
gave 136.6 mg (90%) of 2,3,17-trimethoxy-1,3,5(10),8(14),13(17)-
- \text{pentaene-8-aza-gonane iodide: mp 166-7^\circ}$; \(\text{par (DMSO-d}_6\text{)}\) (Appendix
B, Figure 14): \(\delta 7.01 \text{ (s, 1H)), } \delta 6.86 \text{ (s, 1H)), } \delta 4.92 \text{ (d, 1H), } J=10.5
\text{ Hz), } \delta 4.14 \text{ (s, 3H)), } \delta 3.74 \text{ (s, 6H)), } \delta 1.50 \text{ (m, 1H)); \text{ ir (KBr) (Appendix}
A, Figure 12): \(1580, 1500, 1455 \text{ cm}^{-1}; \text{ uv } \lambda_{\text{max}}^{\text{EtOH}}: 290 \text{ nm (4.58).}
\text{ Anal. Calcd for } C_{19}H_{24}NO_3\text{I: C, 51.81; H, 5.49; N, 3.18. Found: C, 51.65; H, 5.43; N, 3.07.}
\text{Reduction of 2,3,17-trimethoxy-1,3,5(10),8(14),13(17)-penta-
ene-8-aza-gonane iodide (81). To a solution of 0.50 g (1.13 mmol)
of 2,3,17-trimethoxy-1,3,5(10),8(14),13(17)-pentaene-8-aza-gonane iodide
(81) in 50 ml absolute ethanol was added 30 mg (0.79 mmol) of sodium
borohydride in 10 ml absolute ethanol. The resulting solution was
stirred at room temperature for 0.5 hr. The solvent was evaporated at
reduced pressure. The residue was dissolved in 50 ml methylene chloride
and washed twice with 10 ml portions of 5% aqueous sodium bicarbonate
and once with 10 ml water and dried over anhydrous magnesium sulfate.
The drying agent was removed by filtration and the solvent was evaporated
under reduced pressure. The resulting material was dissolved in a
minimum amount of benzene and put on a column of neutral alumina (10 g).
Elution of the column with 325 ml benzene gave 0.10 g (31.1%) of 2,3-
dimethoxy-1,3,5(10),13(17)-tetraene-9\&148-8-aza-gonane (82); mp
135-7^\circ after sublimation at 120^\circ at 0.2 mm Hg; \(\text{par (CDCl}_3\text{) (Appendix B,}
Figure 15): \(\delta 6.73 \text{ (s, 1H)), } \delta 6.68 \text{ (s, 1H)), } \delta 5.53 \text{ (m, 1H)), } \delta 3.91 \text{ (m,}
7H)); \text{ ir (KBr) (Appendix A, Figure 13): } 2910, 2810, 2700, 1675, 1630,
1600, 1525, 767 \text{ cm}^{-1}; \text{ uv } \lambda_{\text{max}}^{\text{EtOH}}: 282 \text{ nm (3.58), 286 nm (3.58).}
\text{ Anal. Calcd for } C_{18}H_{23}NO_2\text{I: C, 75.76; H, 8.12; N, 4.91. Found: C, 75.45; H, 8.13; N, 5.11.}
Elution of the column with 30 ml ethyl acetate gave 0.13 g (36.5%) of 2,3,17-trimethoxy-1,3,5(10),13(17)-tetraene-9β,14β-8-aza-gonane (83): mp 109-110°C, recrystallized from petroleum ether;

pmr (CDCl₃) (Appendix B, Figure 16): δ 6.82 (s, 1H), δ 6.68 (s, 1H), δ 3.89 (m, 9H), δ 3.67 (s, 3H); ir (KBr) (Appendix A, Figure 14):
2900, 2800, 2700, 1690, 1600, 1520, 770 cm⁻¹; uv λmaxEtOH: 282 nm (3.61), 286 nm (3.62).

Anal. Calcd for C₁₉H₂₅NO₃: C, 72.35; H, 7.99; N, 4.44.
Found: C, 72.38; H, 7.89; N, 4.59.

Preparation of 2,3-dimethoxy-17-allyloxy-1,3,5(10),8(14),13(17)-pentaene-8-aza-gonane bromide (84). To a solution of 1.0 g (3.35 mmol) of 2,3-dimethoxy-1,3,5(10),13-tetraene-8-aza-gonane-17-one (58b) in 25 ml dry acetone was added 0.5 ml of allyl bromide. The solution was heated under reflux for 24 hr. Dry ether (25 ml) was added to cause the precipitation of all salts. The solid material was removed by filtration and recrystallized from methanol to give 0.35 g (25%) of 2,3-dimethoxy-17-allyloxy-1,3,5(10),8(14),13(17)-pentaene-8-aza-gonane bromide (84): mp 142-3°C; pmr (DMSO-d₆) (Appendix B, Figure 17): δ 7.04 (s, 1H), δ 6.88 (s, 1H), δ 6.02 (m, 1H), δ 5.24-5.64 (m, 2H), δ 5.00 (m, 2H), δ 3.72 (s, 6H); ir (KBr) (Appendix A, Figure 15): 1600, 1575, 1515 cm⁻¹; uv λmaxEtOH: 290 nm (4.54).

Found: C, 58.56; H, 6.35; N, 3.73.

Attempted rearrangement of 2,3-dimethoxy-17-allyloxy-1,3,5(10),8(14),13(17)-pentaene-8-aza-gonane bromide (84). In a 100 ml round bottom flask, equipped with a condenser and a drying tube, a suspension of 25.6 mg (0.061 mmol) of 2,3-dimethoxy-17-allyloxy-1,3,5(10),8(14),
13(17)-pentaene-8-aza-gonane bromide (84) in 25 ml of dry toluene was heated under reflux for 19 hr. At that time all material had dissolved. The solvent was removed under reduced pressure to give an oil. An infrared spectrum (neat) of the oil was identical to that obtained for 2,3-dimethoxy-1,3,5(10),13-tetraene-8-aza-gonan-17-one (58b).

**Reduction of 2,3-dimethoxy-1,3,5(10),8,11,13-hexaene-8-aza-gonan-17-one perchlorate (56b).** To a rapidly stirred suspension of 1.0 g (2.53 mmol) of 2,3-dimethoxy-1,3,5(10),8,11,13-hexaene-8-aza-gonan-17-one perchlorate (56b) in 30 ml acetonitrile was added 0.25 g of sodium borohydride dissolved in 10 ml water. An immediate change to a dark color was noted for the solution. The reaction mixture was stirred for 0.5 hr. Water (50 ml) and 20% hydrochloric acid (10 ml) was added to the solution. The solution was made basic with saturated sodium hydroxide. The aqueous solution was extracted twice with chloroform; and the combined chloroform extracts were washed with water and dried with anhydrous magnesium sulfate. The drying agent was removed by filtration and the chloroform removed under reduced pressure. The resulting oil was crystallized from ethyl acetate-hexane to give 0.15 g (20%) of 2,3-dimethoxy-1,3,5(10),13-tetraene-8-aza-gonan-17-one (58b), identical in all respects with the material prepared from treatment of the protonated enaminoketone 57b with base.

**Attempted preparation of N-(8-3,4-dimethoxyphenethyl)-1,2,3,4-tetrahydro-pyridin-2,5-dione (50b).** In a 25 ml round bottom flask was combined 5.0 g (19.2 mmol) of N-(8-3,4-dimethoxyphenethyl)-3-amino-cyclopent-2-ene-1-one (37b) and 1.6 g (22.2 mmol) of acrylic acid. The flask was immersed in an oil bath and heated (bath temperature 135°) for 2 hr. The flask was cooled and the contents dissolved in chloroform.
The solution was applied to a column of neutral alumina. The column was eluted with chloroform, the solvent was removed from the eluent under reduced pressure, and the solid was crystallized from isopropanol to give 4.0 g (80%) of the starting material N-(β-3,4-dimethoxyphenethyl)-3-amino-cyclopent-2-ene-1-one (37b), mp 125-7°, identical with an authentic sample.

Preparation of N-(β-3,4-dimethoxyphenethyl)-3-amino-cyclohex-2-ene-1-one (93). To a one neck, 1 l round bottom flask, equipped with a Dean-Stark trap and a condenser, was added 36.2 g (0.20 mol) of β-3,4-dimethoxyphenethylamine, 22.4 g (0.20 mol) of 1,3-cyclohexadione and 500 ml dry benzene. The suspension was stirred magnetically and heated under reflux until the theoretical amount of water was collected. The solution was cooled to room temperature. Anhydrous ether was added dropwise with stirring until precipitation ceased. The yellowish solid was collected by filtration and washed well with anhydrous ether to give 55.0 g (100%) of N-(β-3,4-dimethoxyphenethyl)-3-amino-cyclohex-2-ene-1-one (93): mp 116-9°, recrystallized from xylene; pmr (CDCl₃) (Appendix B, Figure 18): δ 6.75 (m, 3H), δ 5.80 (m, 1H), δ 5.14 (s, 1H), δ 3.88 (s, 6H); ir (KBr) (Appendix A, Figure 16): 1510, 1540, 1575, 3180 cm⁻¹; uv λₘₐₓ (EtOH): 229 nm (3.91), 288 nm (4.54).


Preparation of N-(β-3,4-dimethoxyphenethyl)-1,2,3,4,5,6,7,8-octahydro-quinolin-2,5-dione (94). To a one neck, 1 l round bottom flask, equipped with a Dean-Stark trap and a condenser, was added 18.0 g (65.0 mmol) of N-(β-3,4-dimethoxyphenethyl)-3-amino-cyclohex-2-ene-1-one (93), 10.0 g (0.139 mol) of β-propiolactone and 400 ml xylene. The
reaction mixture was heated under reflux overnight. The solvent was evaporated under reduced pressure. The residue was dissolved in 50 ml of ethyl acetate and chromatographed on a column of neutral alumina. Elution with ethyl acetate and evaporation of the solvent gave a golden oil which was crystallized from ether to give 13.9 g (65%) of N-(β-3,4-dimethoxyphenethyl)-1,2,3,4,5,6,7,8-octahydro-quinolin-2,5-dione as a yellow solid; mp 82.5-83.5°; pmr (CDCl3) (Appendix B, Figure 19): δ 6.74 (s, 3H), δ 3.82 (m, 8H), δ 2.47 (s, 4H); ir (KBr) (Appendix A, Figure 17): 1510, 1605, 1640, 1685 cm⁻¹; uv λmaxEtOH: 230 nm (4.07), 299 nm (4.18).

Found: C, 69.46; H, 7.16; N, 4.22.

Preparation of N-(β-3,4-dimethoxyphenethyl)-1,2-dihydro-pyrindan-2,5-dione (9%). To a 125 ml Erlenmeyer was added 50 ml of dry methylene chloride and 0.87 g (3.6 mmol) of N-(β-3,4-dimethoxyphenethyl)-1,2,3,4-tetrahydro-pyrindan-2,5-dione (50b). Freshly prepared activated manganese dioxide (5.0 g) was added and the slurry was stirred magnetically at room temperature for 5 hr. The solution was filtered through celite, and the filter cake was washed well with methylene chloride. The filtrate was evaporated under reduced pressure and the resulting oil was crystallized from chloroform-hexane to give 0.50 g (57%) of N-(β-3,4-dimethoxyphenethyl)-1,2-dihydro-pyrindan-2,5-dione (25): mp 144-5°; pmr (CDCl3) (Appendix B, Figure 20): δ 7.50 (d, 1H, J=9.0 Hz), δ 3.98 (t, 2H, J=7.0 Hz), δ 3.65 (s, 3H), δ 3.59 (s, 3H), δ 2.83 (t, 2H, J=7.0 Hz), δ 2.28 (s, 4H); ir (KBr) (Appendix A, Figure 18): 1645, 1550, 1510, 1455 cm⁻¹; uv λmaxEtOH: 276 nm (4.26).

Anal. Calcd for C18H19NO4: C, 69.00; H, 6.11; N, 4.47.
Preparation of N-(β-3,4-dimethoxyphenethyl)-1,2,5,6,7,8-hexahydro-quinolin-2,5-dione (96). To a solution of 1.0 g (3.02 mmol) of N-(β-3,4-dimethoxyphenethyl)-1,2,3,4,5,6,7,8-octahydro-quinolin-2,5-dione (94) in 75 ml methylene chloride was added 12.0 g of activated manganese dioxide. The slurry was stirred magnetically for 24 hr at room temperature. The manganese dioxide was removed by filtration and the filter cake was washed well with methylene chloride. Evaporation of the methylene chloride under reduced pressure gave a red oil. The oil was dissolved in boiling methanol, decolorized with charcoal and filtered. On cooling a tan solid crystallized. The solid was collected by filtration and dried to give 0.40 g (40%) of N-(β-3,4-dimethoxyphenethyl)-1,2,5,6,7,8-hexahydro-quinolin-2,5-dione (96): mp 184-185.5°; pmr (CDCl₃) (Appendix B, Figure 21): δ 7.73 (d, 1H, J=9.5 Hz), δ 6.6-6.4 (m, 3H), δ 6.30 (d, 1H, J=9.5 Hz), δ 4.33 (t, 2H, J=6.5 Hz), δ 3.73 (s, 3H), δ 3.67 (s, 3H), δ 2.88 (t, 2H, J=6.5 Hz); ir (KBr) (Appendix A, Figure 19): 1510, 1540, 1590, 1665 cm⁻¹; uv λmax: 227 nm (4.00), 283 nm (4.32).

Found: C, 69.51; H, 6.51; N, 4.14.

Preparation of N-(8-3,4-dimethoxyphenethyl)-2,5-dichloro-7,8-dihydro-quinolinium perchlorate (97). A solution of 1.0 g (3.06 mmol) of N-(8-3,4-dimethoxyphenethyl)-1,2,5,6,7,8-hexahydro-quinolin-2,5-dione (96) in 20 ml phosphorus oxychloride was heated under reflux for 0.5 hr. Immediately on heating, the reaction mixture became deep red in color. The reaction mixture was cooled and the excess phosphorus oxychloride was removed under reduced pressure. The red residue was
dissolved in 20 ml water with heating, decolorized with charcoal and filtered to give a yellow solution. Aqueous perchloric acid (10%) was added dropwise with stirring until precipitation ceased. The mixture was cooled overnight at 0-5° to complete precipitation. The solid was isolated by filtration and recrystallized twice from acetone to give 0.74 g (59%) of N-(β-3,4-dimethoxyphenethyl)-2,5-dichloro-7,8-dihydro-quinolinium perchlorate (97); mp 206-7.5°; pmr (TFA) (Appendix B, Figure 22): δ 8.25 (d, 1H, J=9.0 Hz), δ 7.67 (d, 1H, J=9.0 Hz), δ 6.55 (m, 3H), δ 6.21 (t, 1H, J=4.5 Hz), δ 4.73 (t, 2H, J=6.5 Hz), δ 3.51 (s, 6H); ir (KBr) (Appendix A, Figure 20): 1455, 1505, 1575, 1620 cm⁻¹; uv λmax (EtOH): 231 nm (4.10), 252 nm (3.85), 281 nm (4.02), 327 nm (3.80).

Anal. Calcd for C₁₉H₂₀NO₆Cl₂: C, 49.11; H, 4.33; N, 3.01.
Found: C, 49.21; H, 4.46; N, 3.03.
BIBLIOGRAPHY


APPENDIX

Part A. Infrared Spectra
Part B. Proton Magnetic Resonance Spectra
Part C. Mass Spectra
Figure 1 (KBr). N-(3-methoxyphenethyl)-3-amino-cyclopent-2-ene-1-one (37a).
Figure 2 (KBr). N-(3,4-dimethoxyphenethyl)-3-amino-cyclopent-2-ene-1-one (37b).
Figure 3 (KBr). N-(3-methoxyphenethyl)-1,2,3,4-tetrahydro-pyridan-2,5-dione (50a).
A-Figure 4 (KBr). \( \text{N-(\beta-3,4-dimethoxyphenethyl)-1,2,3,4-tetrahydro-pyridin-2,5-dione (50b).} \)
A-Figure 5 (KBr). 3-methoxy-1,3,5(10),8,11,13-hexaene-8-aza-gonan-17-one perchlorate (56a).
Figure 6 (KBr), 2,3-dimethoxy-1,3,5(10),8,11,13-hexaene-8-aza-gonan-17-one perchlorate (56b).
Figure 7 (KBr). 3-methoxy-1,3,5(10),8(14),13(17)-pentaene-8-aza-gonan-17-ol perchlorate (57a).
A-Figure 8 (KBr). 2,3-dimethoxy-1,3,5(10),8(14),13(17)-pentaene-8-aza-gonan-17-ol perchlorate (57b).
**Figure 9 (Neat).** 3-methoxy-1,3,5(10),13-tetraene-8-aza-gonan-17-one (58a).
A-Figure 10 (KBr). 2,3-dimethoxy-1,3,5(10),13-tetraene-8-aza-gonan-17-one (58b).
A-Figure 11 (KBr). 2,3-dimethoxy-1,3,5(10)-triene-9β,13β,14β-8-aza-gonan-17-one (80).
Figure 12 (KBr). 2,3,17-trimethoxy-1,3,5(10),8(14),13(17)-pentaene-8-aza-gonane iodide (81).
Figure 13 (KBr). 2,3-dimethoxy-1,3,5(10),13(17)-tetraene-9β,14β-8-aza-gonane (82).
Figure 14 (KBr). 2,3,17-trimethoxy-1,3,5(10),13(17)-tetrane-9β,14β-8-aza-gonane (83).
A-Figure 15 (KBr). 2,3-dimethoxy-17-allyloxy-1,3,5(10),8(14),13(17)-pentaene-8-aza-gonane bromide (84).
Figure 16 (KBr). N-(8-3,4-dimethoxyphenethyl)-3-amino-cyclohex-2-ene-1-one (93).
Figure 17 (KBr). N-(β-3,4-dimethoxyphenethyl)-1,2,3,4,5,6,7,8-octahydro-quinolin-2,5-dione (94).
A-Figure 18 (KBr). N-(8-3,4-dimethoxyphenethyl)-1,2-dihydro-pyridan-2,5-dione (95).
Figure 19 (KBr). \( \text{N-(8-3,4-dimethoxyphenethyl)-1,2,5,6,7,8-hexahydro-quinolin-2,5-dione (26).} \)
A-Figure 20 (KBr). N-(β-3,4-dimethoxyphenethyl)-2,5-dichloro-7,8-dihydro-quinolinium perchlorate (97).
Figure 2 (CDCl$_3$). N-(O-3,5-dinethoxyphenethyl)-3-amino-cyclopent-2-ene-1-one (37b).
δ-Phenilethylamine (OCDI3)
B-Figure 5(TFA). Crude reaction mixture from the cyclization of N-(2-3-methoxyphenethyl)-1,2,3,4-tetrahydro-pyrindan-2,5-dione (50a).
Figure 6. Crude reaction mixture from the cyclization of 3-(2,3,4-trimethoxyphenethyl)-1,2,3,4-tetrahydro-pyridin-2,5-dione (50b).
Figure 7 (DMSO-d₆). 3-methoxy-1,3,5(10),8,11,13-hexaene-8-aza-gonan-17-one perchlorate (56a).
Figure 8 (DMSO-d$_6$). 2,3-dimethoxy-1,3,5(10),8,11,13-hexa-ene-9-aza-gonan-17-one perchlorate (56b).
Figure 9 (TFA). 3-methoxy-1,3,5(10),8(14),13(17)-pentaene-8-aza-azonan-17-ol perchlorate (57a).
B-Figure 10 (DMSO-d<sub>6</sub>). 2,3-dimethoxy-1,3,5(10),8(14),13(17)-pentaene-8-aza-gonan-17-ol perchlorate (Sb).
Figure 11 (CDCl₃). 3-methoxy-1,3,5(10),13-tetraene-8-azagonan-17-one (58a).
Figure 12 (CDCl₃). 2,3-dimethoxy-1,3,5(10),13-tetraene-8-aza-gonan-17-one (58b).
Figure 13 (CDCl₃, 2,3-dimethoxy-1,3,5(10)-trien-9-one, 139148-8-aza-azonan-17-one (00)).
3-Figure 14 (DMSO-d$_6$). 2,3,17-trimethoxy-1,3,5(10),8(14),13(17)-pentaene-8-aza-gonane iodide (B1).
B-Figure 15 (CDCl₃). 2,3-dimethoxy-1,3,5(10),13(17)-tetraene-98,143-aza-agona (82).
Figure 1: 6 (CDCl₃), 2,3,17-trimethoxy-1,3,5(10),13(17)-tetrabenz-a,g,h,i-azasterane (83).
Figure 17 (DMSO-d6). 2,3-dimethoxy-17-allyloxy-1,3,5(10),
8(14),13(17)-pentasane-8-aza-gonane bromide (84).
Figure 18 (CDCl₃). N-(8-3,4-dimethoxyphenethyl)-3-amino-cyclohex-2-ene-1-one (93).
Figure 19 (CDCl₃). \( N-(8\text{-}3,4\text{-}dimethoxyphenethyl})-1,2,3,4,5,6,7,8\text{-}octahydro-quinolin-2,5-dione \).
Figure 20 (CDCl₃). N-(β-3,4-dimethoxyphenethyl)-1,2-dihydropyrindan-2,5-dione (95).
B-Figure 21 (CDCl₃). \( N-(3,4\text{-dimethoxyphenethyl})-1,2,5,6,7,8\text{-hexahydro-quinolin-2,5-dione} \) (96).
Figure 22 (TFA). N-(8-3,4-dimethoxyphenethyl)-2,5-dichloro-7,8-dihydro-quinolinium perchlorate (92).
Figure 1. 3-Methoxy-1,3',5(10),13,17-penta-aza-14-benzon-17-one (58a).

m/z: 300, 269, 300.
C-Figure 2. 2,3-dimethoxy-1,3,5(10),13-tetraene-8-aza-gonan-17-one (58b).
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C-Table 1. 3-methoxy-1,3,5(10),13-tetraene-8-aza-gonan-17-one (58a).

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C-Table 2. 2,3-dimethoxy-1,3,5(10),13-tetraene-8-aza-gonan-17-one (58b).
BIOGRAPHICAL DATA

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