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PART I. DEAMINATION OF 1-AMINO-4-
BROMO-7,7-DIMETHYLBICYCLO[2.2.1]HEPTAN-
2-OL. PART II. A CYCLIC HYDROXAMIC ACID
FROM 1,3-CYCLOHEXANEDIONE AND
β-NITROSTYRENE.

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PART I. DEAMINATION OF 1-AMINO-4-BROMO-7,7-
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PART II. A CYCLIC HYDROXAMIC ACID FROM 1,3-
CYCLOHEXANEDIONE AND β-NITROSTYRENE

A DISSERTATION SUBMITTED TO THE GRADUATE DIVISION OF THE
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OF THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN CHEMISTRY

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By

Thean-Chit Ooi

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ABSTRACT

PART I. Deamination of 1-amino-4-bromo-7,7-dimethylbicyclo[2.2.1]heptan-2-ol.

PART II. A Cyclic Hydroxamic Acid From 1,3-Cyclohexanedione and β-Nitrostyrene.

PART I

Deamination of 1-amino-4-bromo-7,7-dimethylbicyclo[2.2.1]heptan-2-ol (1) with nitrous acid formed 4-bromo-5,5-dimethylbicyclo[2.1.1]hexane-1-carboxaldehyde (2). The structure of 2 was elucidated with infrared and nmr spectra. The corresponding carboxylic acid, semicarbazone, and p-toluenesulfonylhydrazone derivatives of 2 were prepared.

\[ \begin{align*}
1 & : \begin{array}{c}
\text{N}
\text{H}_2
\text{O}
\text{H}
\end{array} \\
& : \begin{array}{c}
\text{N}
\text{H}_2
\text{O}
\end{array}
\end{align*} \]

\[ \begin{align*}
2 & : \begin{array}{c}
\text{C}
\text{H}
\text{O}
\end{array} \\
& : \begin{array}{c}
\text{C}
\text{H}
\text{O}
\end{array}
\end{align*} \]

\[ \begin{align*}
3 & : \begin{array}{c}
\text{N}
\text{H}_2
\text{O}
\text{H}
\end{array} \\
& : \begin{array}{c}
\text{N}
\text{H}_2
\text{O}
\end{array}
\end{align*} \]

The ring contraction during the deamination of 1 is similar to that of 1-amino-3,3-dimethylbicyclo[2.2.1]heptan-2-ol (3), which formed 5,5-dimethylbicyclo[2.1.1]hexane-1-carboxaldehyde (4). Compounds 1 and 3 are different in the configuration of the hydroxyl groups and the substitution feature at C-3. Therefore, the successful deamination of 1...
and 3 to the bicyclo[2.1.1]hexane derivatives demonstrates that the deamination of 1-aminobicyclo[2.2.1]heptan-2-ols may be of general utility. During the ring contraction, the migrating group is anti-coplanar to the leaving group.

PART II

Condensation of β-nitrostyrene with 1,3-cyclohexanedione in the presence of sodium methoxide did not yield a normal Michael addition product. The product was proved, with the support of spectral data, to be N-hydroxy-3-phenyl-4,5,6,7-tetrahydrooxindol-4-one (5). The acetyl derivative of 5, which gave a band in the infrared spectrum that is characteristic of an ester, ruled out the isomeric structure 6 as an alternative structure for 5.

Upon hydrolysis, compound 5 could be converted into keto acid 7, from which a known compound, 2-phenyloctanedioic acid, could be obtained through Wolff-Kishner reduction. Hydrogenation of 5 over Raney nickel catalyst produced 3-phenyl-2,3,4,5,6,7-hexahydroindol-4-one (8), which was then
dehydrogenated with Raney nickel in hot ethanol to form 3-phenyl-4,5,6,7-tetrahydroindol-4-one (9). Structures 8 and 9 were fully elucidated, and an authentic sample of 9 was synthesized.

Stetter and Hoehne proposed oxazine 10 as the structure of the condensation product. This structure is reassigned as 9.
ACKNOWLEDGMENT

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1. Infrared Spectrum of 4-Bromo-5,5-dimethyl-bicyclo[2.1.1]hexane-1-carboxaldehyde.
5. Infrared Spectrum of 4-Bromo-5,5-dimethyl-bicyclo[2.1.1]hexane-1-carboxylic Acid.
INTRODUCTION

A. Deamination of Bridgehead Substituted Amines

Bridgehead amines have been reported to deaminate readily. Bartlett and Knox\textsuperscript{1} deaminated apocamphyl amine (1) to form its corresponding acetate (2) in 60\% yield. 1-Norbornanol (3) could be obtained in high yield from its related amine.\textsuperscript{2} In addition, compounds 4--7 were easily deaminated to their bridgehead alcohols or acetates without rearrangement.\textsuperscript{3}

\begin{align*}
\text{NH}_2 & \quad \text{HONO} \quad \text{AcOH} \\
\text{NH}_2 & \quad \text{OAc}
\end{align*}

\begin{align*}
1 & \quad 2 \\
3 & \quad 4 \quad R=H \\
5 & \quad R=CH_3 \\
6 & \quad X=H \\
7 & \quad X=NH_2
\end{align*}

The deamination reactions mentioned above gave unarranged products. Some bridgehead substituted amines, such \textsuperscript{8, 4} \textsuperscript{9, 3} and \textsuperscript{10, 5} each of which possessed an active functional
group on a carbon adjacent to the amino-substituted bridgehead, reacted to give partly or completely rearranged products.

\[
\text{NH}_2 \quad \text{O} \quad \overset{\text{NaNO}_2}{\text{AcOH-H}_2\text{O}} \quad \text{N} \quad \text{OH} \quad \text{CO}_2\text{H}
\]

The deamination of 10, which led to the ring contraction product 11, is especially of interest. The migrating group is a tertiary alkyl group, which is well established for its tendency to migrate. The rearrangement might thus be due to the fortunate choice of the model.
The primary objective of the present research is to determine the scope of the reaction with compound 12, which is an amino alcohol similarly constituted as compared to 11 but unsubstituted at C-3.

B. Syntheses of Bicyclo[2.1.1]hexane Ring System

The most direct route to the bicyclo[2.1.1]hexane ring system is by photocycloaddition. Srinivasan\textsuperscript{6} reported that the gas-phase, mercury-sensitized irradiation of 1,5-hexadiene produced bicyclo[2.1.1]hexane along with other products. Liu and Hammond\textsuperscript{7} obtained a bicyclo[2.1.1]hexane derivative from the photosensitized cyclization of myrcene (13). Other methods, such as the photolyses of cyclic ketones (e.g. 14)\textsuperscript{8} and diazoketones (e.g. 15)\textsuperscript{9} were also extensively used.

\begin{equation}
\text{hv} \quad \text{Hg} \quad \text{hv}
\end{equation}

\begin{equation}
\text{13}
\end{equation}
All the above methods were photochemical reactions. The earliest nonphotochemical synthesis of this system, observed by Brown,\textsuperscript{10} was the reaction of keto tosylate 16 with potassium t-butoxide to give a low yield (8\%) of the internal alkylation product 17. McDonald and Reineke\textsuperscript{11} reported the formation of bicyclo[2.1.1]hexane derivatives from acetolysis of bicyclo[2.2.0]hexane tosylate 18. Cairncross,\textsuperscript{12} Pomerantz,\textsuperscript{13} and their co-workers achieved syntheses of the bicyclo[2.1.1]hexane system by the cyclo-addition of olefins to bicyclo[1.1.0]butane derivatives,
Another nonphotochemical method of synthesis was developed in this laboratory. This involved a ring contraction during the deamination of amino alcohol to form in good yield. The present research is the second example of this method of synthesis.

Long after our present research was completed, two independent research groups reported their observations on the conversion of the pinane skeleton into the bicyclo-[2.1.1]hexane ring system. The conversion involved pinacol-type rearrangement closely related to our studies. Suga and coworkers treated cis-α-pinene glycol monotosylate (20) with methanolic potassium hydroxide and obtained 50% yield of 2α-acetyl-5,5-dimethylbicyclo[2.1.1]hexane (21). Carlson and coworkers, on the other hand, obtained 60% yield of 21 by treating 20 with potassium t-butoxide. Both groups
arrived at the same conclusion that the reactive conformer in this reaction was 22.
II. EXPERIMENTAL

All melting points were taken with calibrated total immersion thermometers. Infrared spectra of samples in potassium bromide were recorded on a Beckman IR-5 infrared spectrophotometer. The intensities of the infrared absorption bands were designated as follows: vs, very strong; s, strong; m, medium; and w, weak. The ultraviolet spectrum of a compound in 95% ethanol was obtained with a Cary Model 14 recording spectrophotometer. Nuclear magnetic resonance spectra were determined at 60 Mc with a Varian Associates Model A-60 spectrometer. All nmr solutions were prepared with deuteriochloroform as solvent. Elemental analyses were performed by Dr. A. Bernhardt, Microanalytical Laboratories, Max Plank Institute, Mulheim, West Germany.

A. Deamination of 1-Amino-4-bromo-7,7-dimethylbicyclo[2.2.1]-heptan-2-ol (12)5

The amino alcohol 12 (1.21 g, 0.00518 mole) was dissolved in 20 ml of 50% acetic acid in a 500 ml, 3-necked, round-bottomed flask. The deamination was done under nitrogen at a temperature of 0-5°, which was maintained by an ice bath. A magnetic stirrer was used to provide efficient stirring. Sodium nitrite (2.76 g, 0.04 mole) was dissolved in water (10 g) to give a 4 molal solution, and 7.5 ml of the solution was added dropwise to the amino alcohol in 10 minutes. After the addition was completed, the cold reaction solution was stirred for 20 minutes.
The excess acid was neutralized with a saturated aqueous solution of sodium carbonate monohydrate (9.5 g). The addition should be slow since the evolution of carbon dioxide was vigorous. The yellow product was then filtered while cold and was washed thoroughly with cold water to remove inorganic materials. The crude product was dried in a vacuum desiccator, and sublimed in a sublimation apparatus, at 1 mm Hg pressure and 60-70°. Most of the material sublimed in 1 hour. The sublimate amounted to 0.74 g (66% yield).

Recrystallizations from low boiling petroleum ether (30-60°) afforded 4-bromo-5,5-dimethylbicyclo[2.1.1]hexane-1-carboxaldehyde (30), mp 125-127°, with sublimation (bath preheated to 120°). In contrast to the analog, 5,5-dimethyl bicyclo[2.1.1]hexane-1-carboxaldehyde, the aldehyde 30 did not undergo oxidation readily while stored in a vial, but it was unstable to light.

The infrared spectrum of 30 showed the following characteristic bands: 2801 (w), 2710 (w), and 1704 (s) (the three bands were due to the CHO group), and 1385 (m) and 1374 (m) cm\(^{-1}\) (gem-dimethyl group). The infrared spectrum is shown in Fig. 1.

The nuclear magnetic resonance (nmr) spectrum of 30 showed signals at \(\delta\) 0.96 (singlet, C-5-endo CH\(_3\)), 1.32 (singlet, C-5-exo CH\(_3\)), 1.73 (doublet, \(J=7.5\) cps, C-6-endo proton), 2.72 (a pair of multiplets, \(J=7.5\) cps, C-6-exo
proton), and 9.58 ppm (singlet, C-1 CHO). The nmr spectrum of 30 is shown in Fig. 2.

Anal. Calcd for C_{9}H_{13}BrO (mol wt=217.1): C, 49.79; H, 6.04; Br, 36.81. Found: C, 49.72, 49.67; H, 5.89, 6.00; Br, 37.10, 36.91.

B. 4-Bromo-5,5-dimethylbicyclo[2.1.1]hexane-1-carboxaldehyde Semicarbazone^5

The amino alcohol ^12 (1.21 g, 0.00518 mole) was deaminated according to the usual procedure described previously. The crude deamination product was filtered, washed with cold water, and dissolved in absolute ethanol (4 ml). A hot, saturated, aqueous solution of semicarbazide hydrochloride (0.669 g, 0.006 mole) was added, with swirling. It was followed by a hot, aqueous solution of sodium acetate trihydrate (0.816 g, 0.006 mole).

The mixed solution was warmed for 10 minutes and left to stand at room temperature until cool. Enough cold water was added until the solution became cloudy. The flask was cooled thoroughly in ice, and the solid was filtered. The white semicarbazone (0.64 g) was obtained in 45% yield (based on the amount of the amino alcohol used). The pure compound was obtained by recrystallization from absolute ethanol, mp 147-148°, with decomposition (bath preheated to 140°).

The infrared spectrum of the semicarbazone showed the following characteristic bands: 3449 (sharp, m), 3125-3226 (broad, m), and 1686 (s) (all the three bands were due to
Fig. 1. Infrared Spectrum of 4-Bromo-5,5-dimethylbicyclo[2.1.1]hexane-1-carboxaldehyde.
Fig. 2. Nmr Spectrum of 4-Bromo-5,5-dimethylbicyclo[2.1.1]hexane-1-carboxaldehyde in CDCl₃.
NHCONH$_2$), and 1387 (w) and 1374 (w) cm$^{-1}$ (gem-dimethyl group). The infrared spectrum is shown in Fig. 3.

Anal. Calcd for C$_{16}$H$_{16}$BrN$_3$O (mol wt=274.2): C, 43.79; H, 5.78; N, 15.32 Found: C, 43.80, 43.99; H, 5.79, 5.83; N, 15.50, 15.56.

C. 4-Bromo-5,5-dimethylbicyclo[2.1.1]hexane-1-carboxaldehyde p-Toluenesulfonylhydrazone$^{16}$

Crude aldehyde 30 was prepared from nitrous acid deamination of the amino alcohol 12 (1.21 g, 0.00518 mole), using the usual procedure. The aldehyde was dissolved in a minimum amount of absolute methanol. The hot aldehyde solution was added to a hot methanol solution of p-toluensulfonylhydrazone (0.96 g, 0.00518 mole). The mixed solution was warmed at about 60$^\circ$ in a water bath for 20 minutes. Water was added with swirling until the solution became turbid. The flask was cooled thoroughly before the precipitate was filtered. Crude p-toluensulfonylhydrazone derivative (1.44 g) was obtained in 72.5% yield (based on the amino alcohol 12).

An analytical sample was prepared by several recrystallizations from absolute methanol. It melted at 133-133.5$^\circ$ with decomposition, evolving a stream of colorless gas, and forming a black tarry liquid.

The infrared spectrum of the p-toluensulfonylhydrazone showed absorptions at 3195 (sharp, m) 1319 (s), and 1166 (s) (all the three bands were due to the sulfonamide group), and 1389 (w) and 1376 (w) cm$^{-1}$ (gem-dimethyl group). The infrared spectrum is shown in Fig. 4.

Anal. Calcd for C$_{16}$H$_{21}$BrN$_2$O$_2$S (mol wt=385.4): C, 49.87; H,
Fig. 3. (Upper) Infrared Spectrum of 4-Bromo-5,5-dimethylbicyclo[2.1.1]hexane-1-carboxaldehyde Semicarbazone.

Fig. 4 (Lower). Infrared Spectrum of 4-Bromo-5,5-dimethylbicyclo[2.1.1]hexane-1-carboxaldehyde p-Tolunesulfonylhydrazone.
5.49; Br, 20.73. Found: C, 50.21, 50.07; H, 5.49, 5.36; Br, 20.99, 21.01.

The p-toluenesulfonylhydrazone derivative (1.42 g, 0.0037 mole) was converted into its salt with metallic sodium (0.085 g, 0.0037 mole) in 4 ml of redistilled ethylene glycol (bp 195-197°). The salt was decomposed[17] at 150° in a microdistillation apparatus. There was a great deal of decomposition, but no distillate was collected, even when the bath was heated up to 190°.

D. 4-Bromo-5,5-dimethylbicyclo[2.1.1]hexane-1-carboxylic Acid


Aldehyde 30 was freshly prepared by deaminating the amino alcohol 12 (1.21 g, 0.00518 mole). It was added to a solution containing sodium hydroxide (0.40 g in 10 ml of water) and hydrogen peroxide (4 ml of a 30% solution). The mixture was warmed to 65° in a water bath for 20 minutes. During the period of warming, 6 ml additional 30% hydrogen peroxide was added in 3 portions.

Some yellow solid floated on the surface of the alkaline solution. The solution was filtered and acidified with formic acid solution (1 ml of 98% formic acid in 9 ml of water). A very small amount of the product was obtained. This method of oxidation was abandoned.

2. Potassium Permanganate Oxidation Method[18]

a) The amino alcohol 12 (1.21 g, 0.00518 mole) was used to prepare aldehyde 30. The crude aldehyde, 4 ml of water, and 50 ml of redistilled acetone were placed in a 200-ml, round-bottomed flask. Reagent acetone was distilled
from a small amount of potassium permanganate. Powdered potassium permanganate (0.82 g, 0.0052 mole) was added with swirling in small portions over 30 minutes. At the end of the oxidation, warming in a hot water bath was necessary to complete the oxidation. Enough time was allowed for the oxidation before a drop of glycerol was added to destroy the excess permanganate.

After the solvent was evaporated under reduced pressure, 20 ml of a potassium hydroxide solution (0.5 g in 60 ml of water) was used to tiriturate the paste and filtered. This was repeated twice. The three portions of filtrate were combined and acidified with dilute hydrochloric acid to Congo Red reaction. The flask was cooled thoroughly in an ice bath to coagulate the product. The product was filtered, washed with cold water, and dried in a desiccator. By sublimation at 60-80° and 1 mm Hg pressure, 0.51 g of product 31 was obtained. The yield was 42.5% of the theoretical yield based on the amino alcohol 12. After several recrystallizations from low boiling petroleum ether, the acid melted at 136-139°. The compound did not analyze satisfactorily.

The infrared spectrum of the acid 31 showed characteristic absorption bands at: 2500-3333 (broad, m) and 1684 (s) (both due to CO₂H), and 1391 (w) and 1376 (w) cm⁻¹ (both due to gem-dimethyl group). The infrared spectrum is shown in Fig. 5.
Fig. 5. Infrared Spectrum of 4-Bromo-5,5-dimethylbicyclo[2.1.1]hexane-1-carboxylic Acid.
The nmr spectrum signals of compound 31 were at: $\delta$ 0.95 (singlet, C-5-endo CH$_3$), 1.28 (singlet, C-5-exo CH$_3$), 1.80 (doublet, $J=7.5$ cps, C-6-endo proton), 2.07 (multiplet, C-2 and C-3 methylene protons), 2.65 (a pair of multiplets, $J=7.5$ cps, C-6-exo proton), and 11.28 ppm (singlet, C-1 CO$_2$H). The nmr spectrum is shown in Fig. 6.

b) In one case of the permanganate oxidation, the work-up of the oxidation product was different from that used in part a). Hot water instead of potassium hydroxide was used to triturate the paste. The filtrate gave crystals before acidification; this crop was filtered. The infrared spectrum of this product showed bands at: 2500-3333 (broad, m) and 1681 (s) (both due to CO$_2$H), and 1582 (s) and 1427 (s) cm$^{-1}$ (both due to CO$_2$K).

The filtrate from the above treatment was acidified and cooled in an ice bath. The product was filtered, washed, and dried. After sublimation, with conditions similar to those used in part a), the yield obtained was 18%, mp 129-133°. Elemental analyses were not satisfactory. The infrared spectrum was identical with that obtained for part a).

The above procedure was used before using procedure a). The low yield of the acid 31 and the isolation of the mixture of acid and salt caused us to change the work-up procedure to that used in part a).

c) In another permanganate oxidation reaction, procedure a) was followed, but a different purification method was
Fig. 6. Nmr Spectrum of 4-Bromo-5,5-dimethylbicyclo[2.1.1]hexane-1-carboxylic Acid in CDCl₃.
used. After sublimation, the product was dissolved in ether, extracted with potassium hydroxide solution. The yield was 23% (0.28 g) based on the amount of the amino alcohol used. Recrystallization was done from aqueous ethanol medium, the product thus obtained melted at 158-159°.

The infrared spectrum of this compound (38) showed bands at: 2500-3333 (broad, m) and 1669 (both due to the conjugated CO₂H), 1647 (m), and 1500 (s) cm⁻¹. The ultraviolet spectrum showed absorption maximum at 294 μμ (ε 8750). The nmr spectrum, taken with a low concentration sample, showed that the number of peaks and intensities increased around δ 1.6-1.9 ppm (allylic protons) compared with those of the acid 31. There was no peak at higher field than this. Gem-dimethyl singlets were not observed.


E. Attempts to Synthesize 1-Bromo-7,7-dimethylbicyclo[2.2.1]-heptan-2-ol (50)

1. Conversion of 2-Oxo-7,7-dimethylbicyclo[2.2.1]heptane-1-carboxylic Acid (51) into 1-Bromo-7,7-dimethylbicyclo[2.2.1]heptan-2-one (53)

a) The procedure developed by Meek and Osuga¹⁹ was followed. A suspension of mercuric oxide (3.04 g, 0.014 mole) in 10 ml of 1,1,2,2-tetrachloroethane (TC) was placed in a 200-ml, 3-necked, round-bottomed flask, which was
equipped with a dropping funnel, a reflux condenser, and a stirrer. A solution of the acid 51 (4.61 g, 0.0253 mole), liquid bromine (4.05 g, 0.0253 mole), and 10 ml of TCE was added dropwise, with stirring, during 45 minutes of addition. The reaction was slightly exothermic, so the temperature was kept at 40-50° by using a water bath. The mixture was stirred until the evolution of carbon dioxide ceased.

The red mercuric oxide turned yellow when the addition was almost completed. It became a white suspension (HgBr₂) finally. The test for carbon dioxide with calcium hydroxide solution showed that carbon dioxide was still evolving. The water bath temperature was raised to 60-65° for 30 minutes. After cooling in an ice bath, the solid of mercuric bromide was filtered, and was washed with TCE.

The filtrate was evaporated, and the residue was recrystallized from aqueous ethanol medium. A product, mp 160-170°, was obtained in 9% yield. The material was recrystallized from low boiling petroleum ether to give a product, mp 170-179°, which showed one carbonyl band at 1754 cm⁻¹ in the infrared spectrum. After sublimation, at 1 mm Hg pressure and 45-80° (bath temperature), and several recrystallizations from low boiling petroleum ether, an analytical product of bromo ketone 53 was obtained (mp 193-195°).

**Anal. Calcd for C₉H₅BrO (mol wt=217.1):** C, 49.78; H, 6.03; Br, 36.80. **Found:** C, 49.92, 49.94; H, 6.06, 6.00; Br, 36.78)
Reduction of 53 to form bromo alcohol 50 was deferred due to insufficient bromo ketone 53 and the shortage of keto acid 51.

b) Before the method used in part a) was done, the method by Wilder and Winston20 was tried for the conversion of 51 into 53. The keto acid 51 (2.75 g, 0.0151 mole) was dissolved in excess warm ammonium hydroxide. Ammonia was evaporated until the keto acid began to precipitate. A few drops of ammonia was then added to redissolve the precipitate.

A solution of aqueous silver nitrate (2.56 g, 0.0151 mole) was added dropwise with stirring to the hot ammoniacal solution. After the solution was cooled, not much suspension of silver salt appeared. The solvent was thus evaporated, and the slurry material was cooled and filtered. The solid was washed successively with water, alcohol, and ether. The yield was low (10%), and the product (silver salt of 51) was colored and difficult to purify. An attempt to convert the silver salt of 51 into 53 was not made.

2. Attempted Reduction of 2-Oxo-7,7-dimethylbicyclo[2.2.1]heptane-1-carboxylic Acid (51) to 2-Hydroxy-7,7-dimethylbicyclo[2.2.1]heptane-1-carboxylic Acid (54)

Compound 51 (2.75 g) was placed in the container of a Parr hydrogenation apparatus, with platinum oxide (0.5 g) and absolute ethanol (150 ml). Reduction was attempted at
45-50 psi and room temperature for 18 hours. Not much pressure drop was observed. After the usual work-up, the compound isolated had mp 235-237°, and its infrared spectrum showed the presence of two carbonyl groups at 1745 and 1686 cm\(^{-1}\). This was the starting material, 51, (lit.\(^2\) mp 234°; ir: 1751 and 1692 cm\(^{-1}\)). The method was abandoned.
III. DISCUSSION AND RESULTS

A. Synthesis of 1-Amino-4-bromo-7,7-dimethylbicyclo[2.2.1]heptan-2-ol (12)

The synthesis of amino alcohol 12 was accomplished in this laboratory. In this synthesis, cyano compound 23 was the important intermediate, which could be obtained from camphor through several reactions as shown below.

\[
\begin{array}{c}
\text{O} \\
\text{NH}_2\text{OH} \\
\text{H} \\
\end{array} 
\xrightarrow{\text{1. KOBr, OH}^-} 
\begin{array}{c}
\text{NOH} \\
\text{Br} \\
\text{Br} \\
\text{0} \\
\end{array} 
\xrightarrow{\text{2. (O}_2\text{) air}} 
\begin{array}{c}
\text{NO}_2 \\
\text{Br} \\
\text{Br} \\
\text{CN} \\
\text{OH} \\
\end{array}
\]

Usual hydrolytic procedures failed to hydrolyze 23 to 24; this was, however, accomplished with alkaline hydrogen peroxide. Treatment of 24 with alkaline sodium hypobromite produced 25, instead of the desired 12. The conversion of 25 into 12 proved to be arduous.
Hydrolytic experiments of 22, with both acids and bases, were not successful to obtain 12. However, hydrazine cleaved the heterocyclic ring of 25 effectively, and formed 26. The semicarbazide 26 was converted into the semicarbazone 27. Oxidation of 27 with lead tetraacetate formed 28 instead of the expected azoacetate. The infrared spectrum of this product showed a carbonyl band at 1701 cm\(^{-1}\), and the nmr spectrum showed a singlet at \(\delta 1.68\) ppm which was assigned to the six protons of the gem-dimethyl group. Structure 28 is consistent with these data. The isomeric compound 29 was not isolated. A recent report, which appeared after our work was complete, indicated that oxidation of semicarbazones with
lead tetraacetate led to O to C cyclization products, i.e. compounds of type 29. Factors that determine which cyclization occurs, N to C (28) or O to C (29), are not known.

Compound 28 hydrolyzed easily to 12, with 0.4 N hydrochloric acid at room temperature for three hours. The hydroxyl group of compound 12 should be exo as this stereochemistry was assigned to compound 23.23

B. Deamination of 1-Amino-4-bromo-7,7-dimethylbicyclo[2.2.1]heptan-2-ol (12)

Deamination of amino alcohol 12 with sodium nitrite solution in glacial acetic acid formed aldehyde 30, in 66% yield. However, the yields of the aldehyde were variable. In one experiment, when the crude aldehyde was used to prepare its p-toluenesulfonylhydrazone derivative, the derivative was obtained in 72.5% yield, based on the amount of the amino alcohol used. In contrast to analog 11, aldehyde 30 was not susceptible to rapid air oxidation; but 30 was unstable to light.
The best way to identify the bicyclo[2.1.1]hexane ring system is by comparisons of the nmr spectra of the aldehyde (Fig. 2) and its acid (Fig. 6) with the published spectra of closely related compounds.5, 8, 26, 27

The chemical shifts of C-2, C-3, and C-6 methylene protons of the compounds listed in Table I show that a formyl or carboxyl group at the bridgehead causes a long-range deshielding effect on these protons. A bromo substituent at the bridgehead has a similar deshielding effect. Chemical shifts of these protons for compounds 11, 30, and 31 demonstrate that the deshielding effect of the bromo

substituent is much more prominent on C-6 methylene protons than on C-2 and C-3 methylene protons. It is interesting to note that, because of the presence of the bromo group, in compounds 11, 34, 35, 36, and the corresponding acid of 11, is in between the two methyl singlets. The proton of
Table I. Nmr Spectra of Some endo-exo

<table>
<thead>
<tr>
<th>endo-exo</th>
<th>C-5-endo</th>
<th>C-5-exo</th>
<th>C-6-endo H</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CH₃</td>
<td>CH₃</td>
<td>( &amp; C-5-endo H)</td>
</tr>
<tr>
<td>11</td>
<td>0.92 (s)</td>
<td>1.28 (s)</td>
<td>1.06 (d)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>J = 7.5</td>
</tr>
<tr>
<td>30</td>
<td>0.96 (s)</td>
<td>1.32 (s)</td>
<td>1.73 (d)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>J = 7.5</td>
</tr>
<tr>
<td>31</td>
<td>0.95 (s)</td>
<td>1.28 (s)</td>
<td>1.80 (d)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>J = 7.5</td>
</tr>
<tr>
<td>33</td>
<td>--</td>
<td>--</td>
<td>0.87 (q)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>( &quot; &quot; )</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.55 (q)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>( &quot; &quot; )</td>
</tr>
</tbody>
</table>

1. Abbreviations: s, singlet; d, doublet; q, quartet; m, constant: cps.
2. The peak position is uncertain since it is very close to
3. K. Ebisu, L. B. Batty, J. M. Higaki, and H. O. Larson,
5. B. J. Lowry, Ph.D. Dissertation, University of
Bicyclo[2.1.1]hexane Derivatives

<table>
<thead>
<tr>
<th>C-6-exo H ( &amp; C-5-exo H)</th>
<th>C-2 &amp; C-3 bridgehead methylene proton or -CHO protons</th>
<th>References</th>
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</thead>
<tbody>
<tr>
<td>2.08 (m)</td>
<td>1.77 (m) 2.33 (b) 9.67 (s)</td>
<td>iii</td>
</tr>
<tr>
<td>2.72 (double m) J=7.5</td>
<td>2.06 (m) --</td>
<td></td>
</tr>
<tr>
<td>2.65 (double m) J=7.5</td>
<td>2.07 (m) --</td>
<td>(11.28 s)</td>
</tr>
<tr>
<td>1.59 (m) (\text{ii}^{\text{iv}})</td>
<td>1.59 (m)(\text{ii}^{\text{iv}}) 2.53 (b) --</td>
<td>iv</td>
</tr>
<tr>
<td>1.9 (-) (\text{ii}^{\text{v}})</td>
<td>1.86 (m) 2.57 (m) --</td>
<td>v</td>
</tr>
</tbody>
</table>

multiplet; b, broad. Chemical shift: \(\delta\) (ppm). Coupling another band.


the aldehyde group of 30, which appears as a singlet, shows that the aldehyde group is attached to a bridgehead carbon (tertiary carbon).

One interesting feature of compound 30 is that all the bicyclic ring carbons are fully substituted except C-2, C-3, and C-6. This constitutes a good model for examining the long-range coupling between C-6 protons and protons on C-2 and C-3 without other interference. In the nmr spectrum of 30 (Fig. 2), the C-6-endo proton coupled (J=7.5 cps) with the C-6-exo proton only. On the other hand, the C-6-exo proton coupled with the C-6-endo proton to a doublet, and further split by the exo protons on C-2 and C-3 to a pair of multiplets. The exact long-range coupling constants were not determined, but the width of the multiplets indicated that they were approximately of the same dimension as reported data.\textsuperscript{12} The long-range coupling constant was reported\textsuperscript{12} to be 2.0 cps for compound 37.
The infrared spectrum of the aldehyde 26 (Fig. 1) showed absorption bands which are characteristic of an aldehyde group (2801, 2710, and 1704 cm⁻¹). The semicarbazone and p-toluenesulfonylhydrazone derivatives of 30 also gave support to the aldehyde structure.

C. Oxidation of 4-Bromo-5,5-dimethylbicyclo[2.1.1]hexane-1-carboxaldehyde (26)

Aldehyde 11 was oxidized to its corresponding acid, by using an aqueous solution of 30% hydrogen peroxide and 5% sodium hydroxide. In the present work, the same method was tried once to oxidize aldehyde 30. However, only a very small amount of product was obtained. Since amino alcohol 12 was so precious, this method was abandoned.

Oxidation with potassium permanganate in aqueous acetone medium was then used. Potassium hydroxide solution was used to work up the oxidation paste. The yield of product 31 (mp 136-139°) after sublimation was 42.5% based on 12. The infrared spectrum of 31 (Fig. 5) showed the typical bands of carboxylic acid (a broad band at 2500-3333, and a strong band at 1684 cm⁻¹) and the two weak bands for the gem-dimethyl group (1376 and 1391 cm⁻¹). The nmr spectrum of 31 (Fig. 6) was similar to that of 30 (Fig. 2) except that in the former, the CO₂H-proton appeared as a singlet at 6 11.28 ppm. The elemental analyses for compound 31 were not satisfactory.

In one case of the permanganate oxidation, hot water instead of potassium hydroxide solution was used to work up
the oxidation paste. After sublimation, the product was extracted with ether and precipitated with potassium hydroxide solution. The potassium salt was acidified with dilute hydrochloric acid, and recrystallized from aqueous ethanol medium. A 23% yield of an acid, mp 158-159°, was obtained. Infrared, ultraviolet, and nmr spectra indicated that the acid was $38$, though the proof of structure was incomplete. Clean separation of the mixture of $31$ and $38$ was not attained.

\[
\begin{align*}
\text{CO}_2\text{H} \\
38
\end{align*}
\]

Wiberg$^{29}$ reported that compound $33$ was dehydrobrominated during a solvolysis reaction. The formation of $38$ in our oxidation reaction could also be rationalized with this reaction. The ultraviolet and nmr spectra indicated that a shift of the exocyclic double bond in $38$ and dimerization$^{28a}$ did not occur. It is noteworthy that the deamination step itself was not impaired by dehydrobromination.
D. Stereochemistry of the Bridgehead Deamination and Related Pinacol-Type Rearrangements

1. The Bridgehead Deamination of 12

Compounds 10 and 12 are similarly constituted. An important difference between them is that C-3 of 10 is disubstituted whereas that of 12 is unsubstituted. Deamination of 12, which led to a ring contraction product 30, is similar to the deamination of 10. This indicated that the presence of two methyl groups at C-3 (tertiary migrating group) is not a factor to govern the path of the rearrangement. In contrast, the presence of a hydroxyl group at C-2 is an important feature in this ring contraction reaction. Electron deficiency at C-2, concurrent with the migration of bond between C-2 and C-3, is relieved by the formation of a carbonyl group following the loss of the hydroxyl proton.

The hydroxyl group in compound 10 was reported to be endo.\(^5\) In compound 12, the hydroxyl group should be exo as this stereochemical arrangement was assigned to its precursor, 23.\(^23\) In spite of this difference, both compounds 10 and 12
gave the same type of rearrangement. Thus, the configuration of the hydroxyl group is not crucial for the success of the reaction, but the presence of the hydroxyl group is necessary.

The elimination of nitrogen from the diazonium salt 39 provided a strong driving force for the following reaction path:

\[
\begin{align*}
\text{HONO} & \rightarrow \begin{array}{c}
\text{Br} \\
\text{OH} \\
\text{NH}_2
\end{array} \\
\text{Br} & \rightarrow \begin{array}{c}
\text{N}_2 \\
\text{H}
\end{array} \\
\text{CHO}
\end{align*}
\]

The migration of bond between C-2 and C-3 to the C-1 bridgehead probably occurred concertedly with, or immediately after the elimination of nitrogen. It is noteworthy that elimination of the bromide ion did not occur during the cleavage of the bond between C-2 and C-3. The 1,2-hydride shift product was not obtained, although the resulting product 40 would be less strained than aldehyde 30. The diol 41 and the acetate 42 were also not detected.
The structure of amino alcohol 12 indicates that the leaving group (or the C-N bond) and the migrating group (or the bond between C-2 and C-3) during the deamination of 12 are anti-coplanar. This feature is a critical requirement for the ring contraction. Similar ring contraction was reported for the deamination of several 2-aminoalcohols.30 For instance, isomers 43 and 44, both with equatorial amino groups and anti-coplanar stereochemistry of the two stated bonds, deaminated to give exclusively the same ring-contraction product. On the other hand, in isomer 45, the amino group is axial and the anti-coplanar bond is the C-H bond at C-1 but not a bond of the ring. Thus, the deamination products contained more than 97% of the ketone resulting from
1,2-hydride shift. Similarly, isomer 46, also with an axial amino group, deaminated to give almost exclusively (more than 98%) the epoxide as shown.

It was reported that when compound 23 was degraded by alkali, cleavage of the bond between C-2 and C-3 occurred. On the other hand, when compound 20 was treated with hydroxy-

lamine, products resulting from cleavage of the bond between C-1 and C-2 were obtained. In the deamination reaction of

neither of these paths was followed. The deamination product indicated that the bond between C-2 and C-3 was cleaved, but the bromine group was not involved in the
cleavage reaction.

2. An incomplete research on pinacol-type rearrangement of 50

Bridgehead halides of bicyclo[2.2.1]hexanes are known for their low reactivity in substitution reactions. Bartlett and Knox\(^1\) reported that chloro compound 47 did not give a precipitate of silver chloride when boiled with aqueous alcoholic silver nitrate for 48 hours. In contrast, chloro compound 48, the open-chain analog of 47, reacted very rapidly with silver nitrate at room temperature. Related bromides are more reactive than the chlorides. For instance, Doering and coworkers\(^3^2\) reported that when 1-bromonorbornane (49) was heated with aqueous silver nitrate at 150\(^\circ\) for 48 hours, partial solvolysis took place.

It was hoped that bromo alcohol 50 would solvolyze under similar conditions to give the ring contraction product 11. This would extend our research on bridgehead deamination to dehydrobromination involving a bridgehead bromo group.
In this solvolysis, the silver ion will facilitate the removal of the bromide ion, thereby initiating a rearrangement that may produce aldehyde 11 or its acid. The stereochemistry of this reaction presumably would be similar to that in the deamination of 10 and 12.

Bromo alcohol 50 could probably be obtained from keto acid 51 through the Hunsdiecker reaction and the reduction of a keto group to an alcohol group. And, the keto acid could be prepared21 from sulfonic acid 52 as shown below.

There are two routes of converting keto acid 51 into bromo ketone 53, namely via silver salt (Hunsdiecker reaction) and mercuric salt (modified Hunsdiecker reaction). The silver salt procedure20 is tedious, since it requires pure and dry silver salt intermediate for further reaction. This
procedure was tried but finally abandoned. The one-step, mercuric salt procedure\textsuperscript{19} was done with success.

\[
\begin{align*}
\text{Br} & \quad \text{CO}_2\text{H} \\
\text{HgO} & \quad \text{AgNO}_3 \\
\text{Br}_2 & \quad \text{NH}_4\text{OH} \\
\text{Br}_2 & \quad 53 \\
53 & \quad 51
\end{align*}
\]

The product \textit{53} gave satisfactory elemental analyses and showed one carbonyl band at 1754 cm\textsuperscript{-1} in the infrared spectrum. It could be expected that this bromo ketone would be reduced to bromo alcohol \textit{50} by catalytic hydrogenation. However, this conversion was temporarily deferred due to insufficient bromo ketone \textit{53} and keto acid \textit{51}.

The above sequence involved the Hunsdiecker reaction prior to reduction. One attempt to convert the keto acid \textit{51} into its corresponding alcohol \textit{54} (reduction prior to the Hunsdiecker reaction) was unsuccessful. The failure was probably due to the presence of the bulky carboxylic group.

\[
\begin{align*}
\text{CO}_2\text{H} & \\
\text{OH} & \\
54
\end{align*}
\]
IV. CONCLUSION

Deamination of amino alcohol 12 with sodium nitrite solution in glacial acetic acid formed a ring-contraction product, aldehyde 30. The structure of 30 was fully elucidated with infrared and nmr spectra. The semicarbazone and p-toluenesulfonylhydrazone derivatives of 30 were prepared. Aldehyde 30 was also oxidized to its acid.

The ring contraction during the deamination of 12 is similar to that of 10 which formed 11. Hence, the two methyl groups at C-3 of compound 10, which constitute a tertiary migrating group, is not essential for the ring contraction. On the other hand, the configuration of the hydroxyl group, which is exo in 12 and endo in 10, is not critical for the success of the reaction; but the presence of the hydroxyl
group is necessary. Therefore, the successful deamination of 10 and 12 to bicyclo[2.1.1]hexane derivatives demonstrates that the deamination of l-aminobicyclo[2.2.1]heptan-2-ols may be of general utility. The important factor that governs the ring contraction is that the migrating group is anti-coplanar to the leaving group. The presence of a bromo group in 12 did not affect the deamination. However, during the oxidation of 30, part of the product was dehydrobrominated to an acid for which structure 38 was tentatively assigned.

\[
\text{Br} \quad \text{CO}_2\text{H} \\
\text{53}
\]

Related to this research, bromo ketone 53 was synthesized. This compound should undergo reduction to its bromo alcohol. It is hoped that solvolysis of the bromo alcohol in the presence of silver nitrate will produce a similar ring contraction. The silver ion will facilitate the removal of bromide ion, thereby initiating a rearrangement that may

\[
\text{Br} \quad \text{CHO} \\
\text{50} \quad \text{12}
\]
form aldehyde 12 or its acid. The aforementioned stereo-
chemical requirement should be possessed by structure 50.
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I. INTRODUCTION

Stetter and Hoehne\textsuperscript{1} reported that the condensation of $\beta$-nitrostyrene with 1,3-cyclohexanedione in the presence of sodium methoxide did not lead to a normal Michael addition product.\textsuperscript{2} The product, which was a 1:1 molar adduct with subsequent elimination of a molecule of water, was formulated as the oxazine $\textsubscript{1}$. The condensation product of 1-nitropropene

\[ \text{3} \]

and 1,3-cyclohexanedione was assumed to be an analog of $\textsubscript{1}$. Nitroethylene, however, reacts with 1,3-cyclohexanedione to form a normal Michael addition product $\textsubscript{2}$.

Compound $\textsubscript{1}$ was reduced\textsuperscript{1} with hydrogen over Raney nickel to $\textsubscript{3}$, which was then dehydrogenated\textsuperscript{1} to form $\textsubscript{4}$. Hydrolysis of $\textsubscript{1}$, in acidic medium, gave keto acid $\textsubscript{5}$, which was further converted into 2-phenyloctanedioic acid.\textsuperscript{1} The dibasic acid had the same melting point as the authentic sample prepared

\[ \text{4} \]
later by another research group by an established method of synthesis.\(^3\)

\[
\begin{align*}
0 & \quad \text{C}_6\text{H}_5 \\
\text{HO}_2\text{C}-\text{(CH}_2\text{)}_3\text{C}-\text{CH}_2\text{-CH-CO}_2\text{H} & \quad \text{5}
\end{align*}
\]

Structures \(1, 3,\) and \(4\) were not accompanied by spectral data. A preliminary examination\(^4\) showed that structure \(1,\) assigned to the condensation product, was not correct, but the investigation did not arrive at correct reassignments of structures \(1, 3,\) and \(4\). Thus the problem of structural determinations for these compounds and the pathway of the reaction leading to the unusual condensation product remained to be solved. This became the objective of this research. A new reaction related to the chemistry of nitro group appeared to be in hand.
II. EXPERIMENTAL

All melting points were taken with total immersion thermometers. Infrared spectra were determined with the compounds in potassium bromide disks on a Beckman IR-5 spectrophotometer. The intensities of infrared absorption bands were designated as follows: vs, very strong; s, strong; m, medium; and w, weak. Ultraviolet spectra of compounds in 95% ethanol were obtained on a Cary Model 14 recording instrument. Nuclear magnetic resonance spectra were taken with Varian Associates Model A-60 and HA-100 spectrometers. Chemical shifts were given in ppm (δ) downfield from tetramethylsilane as the internal reference. Mass spectra were taken with a Hitachi-Perkin-Elmer RMU-6E mass spectrometer. Microanalyses were done by Dr. A. Bernhardt, Microanalytical Laboratories, 5251 Elbach uber Engelskirchen, Fritz-Pregl-Straße 14-16, West Germany, and Berkeley Analytical Laboratory, P. O. Box 150, Berkeley, California, 94701.

A. β-Nitrostyrene

β-Nitrostyrene was prepared according to the procedure of Gairaud and Lappin. Benzaldehyde (100 g, 0.94 mole), nitromethane (100 ml, 1.86 moles), ammonium acetate (40 g), and glacial acetic acid (200 ml) were placed in a 1-liter flask and maintained at gentle reflux for 1.5 hours. The reaction was done in a hood because some oxides of nitrogen
might be evolved. After the reaction was completed, the mixture was cooled and poured into 1 liter of crushed ice and water. The solid was isolated by filtration, and washed with cold water. The dark material was treated with Darco (activated charcoal) and recrystallized from absolute methanol. Yellow crystals were obtained in 52% yield (73.5 g), with mp 57-59° (lit. 6 58-59°). The compound is a skin irritant.

B. 1,3-Cyclohexanedione

Commercial 1,3-cyclohexanedione, supplied by Aldrich Chemical Co., was a sticky, brown material stabilized with 20% aqueous sodium chloride solution. It was freshly purified before using for the following Michael reaction. The material (33 g) was successively extracted with benzene, first 200 ml, followed by 100 ml each time, to a total volume of 700 ml. The benzene extracts were decanted, combined, boiled with Darco for 15 minutes, and filtered. The filtrate was once more treated with Darco and filtered. Most of the solvent was then evaporated under reduced pressure. The residue was dissolved in a minimum amount of benzene, and left to stand overnight at room temperature. After cooling in ice for about 1 hour, the yellow 1,3-cyclohexanedione was collected by filtration (yielded 15.5 g, 47%). It melted at 94-96° (lit. 6 105-106°).

C. N-Hydroxy-3-phenyl-4,5,6,7-tetrahydrooxindol-4-one (6)

The condensation of 1,3-cyclohexanedione and 8-nitrostyrene by sodium methoxide was done according to the
procedure of Stetter and Hoehne.\(^1\)

Sodium metal (0.5 g, 0.0215 mole) was allowed to react with absolute methanol (30 ml) in a 125-ml Erlenmeyer flask. The solution was allowed to cool to room temperature, then 1,3-cyclohexanedione (8.4 g, 0.075 mole) was added with swirling. After solution was attained, \(\beta\)-nitrostyrene (10.85 g, 0.075 mole) was added in small portions. The reaction was exothermic, so the solution was maintained at 35-40° by cooling, until all the solid dissolved. After 15 minutes, a pan of tap water was used to keep the flask at room temperature for 1 hour. The flask was then kept in the refrigerator overnight.

The crude product was filtered and purified promptly to avoid extensive decomposition. It was first triturated with a small amount of absolute methanol, cooled and filtered. Then the product was dissolved in a larger amount of methanol, and the insoluble material was filtered. After several recrystallizations from methanol, white crystals were obtained which melted at 167-168° (lit.\(^1\) 165-167°). The average yield was 45-50%.

A 5% ethanol solution of this compound gave a distinct, purple color within a few seconds after a 1% alcoholic ferric chloride solution was added. The color turned intense purple after 1 minute. With 1% aqueous ferric chloride solution, the purple color developed within 5 minutes. In this case, the color did not turn intense like the former test.\(^7\)
The infrared spectrum showed peaks at: 3333 (s, OH), 2924 (m, C-H), 1698 (m, \(\gamma\)-lactam C=O), 1631 (s, C=O at C-4), and 742 (s) and 697 (s) cm\(^{-1}\) (monosubstituted phenyl group). The infrared spectrum is given in Fig. 1.

The ultraviolet spectrum, shown in Fig. 2, had a maximum at 268 m\(\mu\) (\(\varepsilon\) 10,250).

The nuclear magnetic resonance (nmr) spectrum (100 Mc, DMSO-\(d_6\)) showed resonance at \(\delta\) 2.03 (multiplet, C-6 methylene protons), 2.21 (multiplet, C-5 methylene), 2.69 (multiplet, C-7 methylene), 4.98 (triplet, \(J=2.0\) cps, C-3 proton), 7.24 (singlet, phenyl protons), and 10.20 ppm (singlet, N-OH). The multiplet at \(\delta\) 2.48 was due to the residual protons of the solvent, and the singlet at 3.35 was due to water. By irradiating protons at \(\delta\) 2.69, the triplet at 4.98 became a singlet. The nmr spectrum is shown in Fig. 3.

The molecular ion in the mass spectrum appeared as the most intense peak at m/e 243.

**Anal.** Calcd for C\(_{14}\)H\(_{13}\)N\(_3\)O\(_3\) (mol wt=243.3): C, 69.13; H, 5.38; N, 5.75. Found: C, 69.23; H, 5.43; N, 5.81.

D. **N-Acetoxy-3-phenyl-4,5,6,7-tetrahydrooxindol-4-one** (13)

N-Hydroxy-3-phenyl-4,5,6,7-tetrahydrooxindol-4-one (2.73 g, 0.0112 mole) was reacted with acetic anhydride (1.70 g, 0.0167 mole) in 17 ml of anhydrous pyridine at room temperature. The reaction was exothermic, so a tap water bath was used.
Fig. 1. Infrared Spectrum of N-Hydroxy-3-phenyl-4,5,6,7-tetrahydrooxindol-4-one.
Fig. 2. Ultraviolet Spectrum of N-Hydroxy-3-phenyl-4,5,6,7-tetrahydrooxindol-4-one in 95% Ethanol.
Fig. 3. Nmr Spectrum of N-Hydroxy-3-phenyl-4,5,6,7-tetrahydrooxindol-4-one in DMSO-d$_6$. (a, CHD$_2$SOCD$_3$; b, H$_2$O; c, Spin Decoupling).
After 3 hours, 180 ml of ice water was added, cooled, and the orange produce was filtered. The solid was washed thoroughly with ice water and was recrystallized from ethanol. The yield was 1.23 g (40%) of white crystals with mp 165-166°.

The infrared spectrum showed absorptions at: 3021 (w, aromatic C-H), 2933 (w) and 2874 (w) (aliphatic C-H), 1761 (s, acetoxyl C=O), 1681 (s, amide C=O), 1653 (s, C=O at C-4), and 756 (s) and 700 (s) cm\(^{-1}\) (monosubstituted phenyl group). The infrared spectrum is given in Fig. 4.

The nmr spectrum (100 Mc, CDCl\(_3\)) showed resonances at \(\delta\) 1.82 and 2.12 (both singlets, both due to CH\(_3\)CO), \(\sim\) 2.12 (multiplet, C-6 methylene protons), 2.30 (multiplet, C-5 methylene), 2.71 (multiplet, C-7 methylene), 5.01 and 5.10 (both triplets, both due to C-3 proton), and 7.25 ppm (singlet, phenyl protons). By irradiating protons at 2.71, the two triplets became two singlets. The area ratio of \(\delta\) 1.82 to 2.21 singlets was equal to that of \(\delta\) 5.10 to 5.01 triplets. The nmr spectrum is shown in Fig. 5.

**Anal.** Calcd for C\(_{16}\)H\(_{15}\)NO\(_4\) (mol wt=285.3): C, 67.36; H, 5.30; N, 4.91. Found: C, 67.59, 67.67; H, 5.20, 5.15; N, 4.76, 4.88.

E. **3-Phenyloxyindole**

Mandelanilide, which melted at 149.5-151° (lit.\(^9a\) 151-152°), was obtained from the reaction of equimolar quantities of aniline and mandelic acid.\(^9a\) To prepare 3-phenylxindole, the anilide (15 g) was added within 5 minutes to vigorously
Fig. 4. Infrared Spectrum of N-Acetoxy-3-phenyl-4,5,6,7-tetrahydro-oxindol-4-one.
Fig. 5. Nmr Spectrum of N-Acetoxy-3-phenyl-4,5,6,7-tetrahydrooxindol-4-one in CDCl₃. (a, Spin Decoupling).
stirred concentrated sulfuric acid (80 ml) at room temperature, in a 300-ml, 3-necked flask. The temperature was kept below 40°. Stirring was continued for 10 minutes, then the solution was added to crushed ice (500 g). After 2 hours, the precipitate was collected, washed with water, and recrystallized twice from absolute methanol. The yield was 6.93 g (50%) with mp 184-185°. After two more recrystallizations, a product which melted at 187-188° (lit. 9b 191°) was obtained.

The infrared spectrum showed the following characteristics: 3145 (m, N-H of monosubstituted amide), and 1701 cm\(^{-1}\) (s, C=O of γ-lactam). The nmr spectrum (60 Mc, DMSO-\(d_6\)) showed resonances at \(\delta\) 4.74 (singlet, benzylic proton), a broad multiplet with two tallest peaks at 7.08 and 7.33 (phenyl protons), and 10.61 ppm (broad singlet, N-H). The mass spectrum gave a molecular ion peak at m/e 209 (96.5%) and a base peak at 180.

F. Raney Nickel Catalyst

The Raney nickel catalyst used in the hydrogenation of N-hydroxy-3-phenyl-4,5,6,7-tetrahydrooxindol-4-one was freshly prepared, according to the method developed by Pavlic and Adkins.

Sodium hydroxide (64 g) was dissolved in 250 ml of water, and placed in a 2-liter, 3-necked flask which was equipped with a thermometer and an efficient stirrer. Raney nickel alloy (50 g) was added in small portions so that the
temperature was kept at 50-60°. The addition took about 30 minutes to complete. A cooling bath was used and special caution was paid to the addition of the alloy since the reaction was highly exothermic and the evolution of hydrogen was vigorous. At the end of the reaction, the temperature was maintained at about 50° with a warm-water bath for 1 hour. The stirrer was stopped, and the flask was removed from the water bath. After the solid settled at room temperature, the upper alkaline solution was decanted. The black solid was then transferred to a 1-liter graduated cylinder, and washed thoroughly with distilled water (15 liters) through a siphon. The unreacted alloy was lighter than the nickel catalyst, and was thus carried away with the washed water. The water was then decanted, and the catalyst was removed to a container. In the container, the catalyst was washed with absolute ethanol through several decantations. The catalyst was a black, pyrophoric powder, and was kept under absolute ethanol.

G. 3-Phenyl-2,3,4,5,6,7-hexahydroindol-4-one (3)

The hydrogenation of N-hydroxy-3-phenyl-4,5,6,7-tetrahydrooxindol-4-one (6) was done in a Parr hydrogenation apparatus. Compound 6 (6.0 g) was suspended in 250 ml of absolute ethanol, and hydrogenated over Raney nickel catalyst (ca. 4 g) with hydrogen at 40-50 psi pressure and room temperature. The compound went into solution as the hydrogenation took place. After 6 hours, the catalyst was
filtered, and the solvent was evaporated under reduced pressure. The yellow residue was recrystallized several times from acetone to give a pure, white product (average yield ca. 55%). The melting point was 196-197° (lit. 195-197°).

The product 3 (5% in ethanol) gave a distinct pink color immediately after mixing with 1% of either aqueous or alcoholic ferric chloride solution. 11-15

The infrared spectrum of compound 3 contained characteristic peaks at: 3145 (sharp, m, N-H), 2667-3021 (complex, m, C-H), 1582 (s, C=O at C-4), 1555 (m), 1508-1527 (broad, vs), and 761 (m) and 696 (s) cm⁻¹ (Monosubstituted phenyl group). The infrared spectrum is shown in Fig. 6.

The maximum of the ultraviolet spectrum was at 308 m\(\mu\) (\(\epsilon\) 21,600). There was no change in the spectrum when one or two drops of a 10% aqueous sodium hydroxide solution were added. 13, 16 However, a drop of 6 N hydrochloric acid caused a hypsochromic shift to 293 m\(\mu\) (\(\epsilon\) 17,700). 16 No further change was observed after the second drop of the acid was added. The ultraviolet spectra are shown in Fig. 7.

The nmr spectrum (100 Mc, CDCl₃) showed resonances at: δ 1.95 (multiplet, C-6 Methylene protons), 2.23 (multiplet, C-5 and C-7 methylenes), 6.35 (broad singlet, N-H), 7.15 (multiplet, phenyl protons), and an AMX pattern of peaks due to the C-2 and C-3 protons appeared at 3.29 (quartet, J=5, 11 cps), 3.83 (triplet, J=11, 11 cps), and 4.24 ppm (quartet, J=5, 11 cps). The broad N-H singlet shifted to δ 7.31 when
Fig. 6. Infrared Spectrum of 3-Phenyl-2,3,4,5,6,7-hexahydroazepine.
Fig. 7. Ultraviolet Spectra of 3-Phenyl-2,3,4,5,6,7-hexahydroindol-4-one in: (a) 95% Ethanol (---), and (b) 95% Ethanol + 6 N HCl (----).
the solvent was DMSO-$d_6$. The nmr spectrum is shown in Fig. 8.

In the mass spectrum, the molecular ion occurred as the most intense peak at m/e 213.

**Anal. Calcd for C$_{14}$H$_{18}$NO (mol wt=213.3):  C, 78.85; H, 7.08; N, 6.57. Found:  C, 78.76; H, 7.02; N, 6.58.**

H. 3-Phenyl-4,5,6,7-tetrahydroindol-4-one (4)

3-Phenyl-2,3,4,5,6,7-hexahydroindol-4-one (1 g) was refluxed with Raney nickel catalyst (2 g) in absolute ethanol (50 ml) for 2 hours with efficient stirring. After removing the catalyst by filtration, the solvent was evaporated on a rotatory vacuum evaporator. The residue was recrystallized from absolute methanol. The purified product melted at 238-239° (lit. 239-240°), and amounted to 45% of the theoretical yield. This compound is stable and remains white and crystalline for a long time.

The infrared spectrum of compound 4 had absorption bands at: 3185 (s, N-H), 2933 (m, C-H), 1631 (s, C=O at C-4), 1608 (inflection), 1567 (m), 1529 (m), and 755 (s), and 695 (s) cm$^{-1}$ (monosubstituted phenyl group). The infrared spectrum is shown in Fig. 9.

The ultraviolet spectrum, shown in Fig. 10, exhibited the following set of maxima: 218 m$\mu$ ($\varepsilon$ 22,080), 242 (shoulder, 8450), 263 (10,400), and 287 (shoulder, 6570).

The nmr spectrum (100 Mc, DMSO-$d_6$) showed resonances at $\delta$ 2.04 (multiplet, C-6 methylene protons), 2.36 (triplet, J=6 cps, C-5 methylene), 2.80 (triplet, J=6 cps, C-7 methylene),
Fig. 8. Nmr Spectrum of 3-Phenyl-2,3,4,5,6,7-hexahydropindol-4-one in CDCl₃.
Fig. 9. Infrared Spectrum of 3-Phenyl-4,5,6,7-tetrahydroindol-4-one.
Fig. 10. Ultraviolet Spectrum of 3-Phenyl-4,5,6,7-tetrahydroindol-4-one in 95% Ethanol.
6.91 (doublet, J=2.5 cps, C-2 proton), 7.23 and 7.62 (both multiplets, phenyl protons), and 11.48 ppm (broad singlet, N-H). The multiplet at δ 2.50 was due to the residual protons of the DMSO-d₆, and the singlet at 4.12 was due to water. The nmr spectrum is shown in Fig. 11.

In the mass spectrum of 4, the molecular ion peak, which was also the base peak, appeared at m/e 211.


I. 2-Carbethoxy-3-phenyl-4,5,6,7-tetrahydroindol-4-one (37)

The synthesis of compound 37 was done according to the method of Schoen and Pachter.¹⁷ Ethyl benzoylacetate (19.2 g, 0.1 mole) was dissolved in 30 ml of glacial acetic acid, and cooled to 5°, in a 500 ml, 3-necked, round-bottomed flask. A magnetic stirrer was used to provide efficient stirring. To this solution, a cold, saturated, aqueous solution of sodium nitrite (6.9 g, 0.1 mole) was added, at such a rate that the temperature did not exceed 10°. About 30 minutes was required for the addition. At the end of the addition, the yellow solution solidified. The flask was left to stand for 15 minutes.

1,3-Cyclohexandione (11.2 g, 0.1 mole) solution in glacial acetic acid was then added with swirling. The lumps of isonitrosoketone intermediate dissolved to form a light
Fig. 11. Nmr Spectrum of 3-Phenyl-4,5,6,7-tetrahydroindol-4-one in DMSO-<sub>d6</sub>. (a, Solvent Impurity; b, CH<sub>2</sub>SOCD<sub>3</sub>; c, H<sub>2</sub>O).
brown solution. Stirring was again applied. The cooling bath was replaced with a heating mantle.

Zinc dust (13.1 g, 0.2 g-atom) was added at such a rate that the mixture came to boiling within 3 minutes and boiled actively until all the zinc had been added. The heat of reaction caused the solvent to reflux for 15 minutes. External heating was applied to continue reflux for another 45 minutes. The cooled mixture was poured onto 500 g of ice. The dark-gray material was filtered and recrystallized from absolute ethanol. The yield was 6.02 g (21%, mp 194-195°).

The infrared spectrum of compound 31 showed the following characteristic peaks: 3165 (s, N-H), 2959 (m, C-H), 1689 (s, ester C=O), 1639 (s, C=O at C-4), and 770 (s) and 696 (s) cm^-1 (monosubstituted phenyl group). The infrared spectrum is shown in Fig. 12.

The product 31 was analyzed as a semicarbazone derivative prepared in the following manner. Compound 37 (0.19 g) was dissolved in 3 ml of absolute ethanol. A hot aqueous solution of semicarbazide hydrochloride (0.21 g in minimum amount of water) was added, followed by a hot aqueous sodium acetate solution (0.22 g in minimum amount of water). The mixture was warmed for 10 minutes, and left to stand until cool. White crystals appeared before adding water. Distilled water was added until the solvent became turbid. After thorough cooling, the crystals were filtered and washed with cold water. The crude yield was 0.20 g (88%).
Fig. 12. (Upper) Infrared Spectrum of 2-Carbethoxy-3-phenyl-4,5,6,7-tetrahydroindol-4-one.

Fig. 13. (Lower) Infrared Spectrum of the Authentic Sample of 3-Phenyl-4,5,6,7-tetrahydroindol-4-one.
Recrystallizations from absolute ethanol gave the pure compound, which melted at 275-277° with decomposition. The infrared spectrum of the semicarbazone showed the characteristic bands of the functional groups.

Anal. Calcd for C_{18}H_{20}N_{4}O_{3} (mol wt=340.4): C, 63.52; H, 5.92; N, 16.46. Found: C, 63.46, 63.77; H, 5.78, 5.89; N, 16.16, 16.28.

J. 2-Carboxy-3-phenyl-4,5,6,7-tetrahydroindol-4-one (38)

The ester 37 (5.2 g) was refluxed with a solution of 20 ml of 15% aqueous sodium hydroxide and 40 ml of ethanol for 45 minutes. The ethanol was removed by evaporation under reduced pressure. Solid appeared in the basic aqueous solution. Ice water was added and the solution was acidified with 2 N hydrochloric acid to Congo Red reaction. The white free acid was filtered, washed with water, and pressed dry. For purification, the acid was dissolved in 1 N sodium hydroxide, separated from undissolved material by filtration, precipitated with 2 N hydrochloric acid, and recrystallized from absolute ethanol. After one recrystallization, it yielded 3.73 g (80%) of product. An analytical sample, which melted at 238-239° with decomposition, was obtained by repeated recrystallizations from ethanol.

The infrared spectrum of compound 38 showed characteristic bands at: 2500-3333 (broad, s, N-H, CO_{2}H, C-H), 1637 (broad, s, C=0 at C-4 and CO_{2}H), and 762 (m) and 700 (s) cm^{-1} (monosubstituted phenyl group).
Anal. Calcd for $\text{C}_{15}\text{H}_{13}\text{N}_3\text{O}_3$ (mol wt=255.3): C, 70.58; H, 5.13; N, 5.49. Found: C, 70.59, 70.73; H, 5.09, 5.19; N, 5.49, 5.53.

K. **Authentic Sample of 3-Phenyl-4,5,6,7-tetrahydroindol-4-one (4)**

The carboxylic acid **38** (2.62 g) and 115 ml of light liquid paraffin were placed in a 300-ml, 3-necked, round-bottomed flask. The decarboxylation was done under a nitrogen atmosphere with efficient stirring. The acid dissolved when the temperature was close to the melting point. Carbon dioxide was evolved at 235-245°. After the evolution of gas was almost complete, the temperature was raised to 290-310° for 15 minutes. The mixture was then cooled thoroughly under the nitrogen atmosphere to room temperature, and finally in an ice bath. The solid was filtered, washed with low-boiling petroleum ether, warmed with 1 N sodium hydroxide, filtered, washed with water, and recrystallized from absolute ethanol. The yield was 1.88 g (mp 238-239°) which was 87% of the theoretical yield.

The mixture melting point of this compound (4) with compound **4** from the method of Stetter and Hoehne was 238-239°. The infrared and mass spectra of **4** obtained from the two different sources were identical. The infrared spectrum of the authentical sample **4** is shown in Fig. 13.

The nmr spectrum (100 Mc, DMSO-$d_6$) was essentially identical with that of **4** from the method of Stetter and
Fig. 14. Nmr Spectrum of the Authentic Sample of 3-Phenyl-4,5,6,7-tetrahydroindol-4-one in DMSO-$_d_6$. (a, CH$_2$SOCD$_3$; b, H$_2$O).
Hoehne. The resonance signals appeared at δ 2.03 (multiplet, C-6 methylene protons), 2.37 (triplet, J=6 cps, C-5 methylene), 2.79 (triplet, J=6 cps, C-7 methylene), 6.90 (doublet, J=2.5 cps, C-2 proton), 7.24 and 7.64 (both multiplets, phenyl protons), and 11.48 ppm (broad singlet, N-H). The peaks at δ 2.48 (multiplet) and 3.40 (singlet) were due to solvent residual protons and water respectively. The nmr spectrum of the authentic sample 4 is shown in Fig. 14.


L. 2-Phenylcyclopentanone₁₈

Phenylmagnesium bromide was prepared from clean magnesium ribbon (8.5 g, 0.350 mole) and bromobenzene (55 g, 0.350 mole) in dry ether (400 ml). The reaction was carried out under dry conditions in a 1-liter, 3-necked, round-bottomed flask. The reaction was started by warming a small amount of the ether solution of bromobenzene, a few crystals of iodine, and the magnesium ribbon. After the reaction was started, the bromobenzene solution was added dropwise. Regular reflux was maintained by external heating at the beginning and later by the heat of reaction. The above was done without stirring. At this time, the stirrer was started, and heat was applied to maintain reflux for 30 minutes to complete the reaction.
The reaction mixture was thoroughly cooled and well stirred while an ether (300 ml) solution of 2-chlorocyclopentanone (35 g, 0.295 mole) was added. An orange solution formed with a red liquid on the wall of the flask. The ether was removed by distillation. After adding 150 ml of p-xylene, the reaction mixture was refluxed for 15 minutes.

At this point, the material was dark brown. The mixture was cooled and poured onto ice and dilute hydrochloric acid. Enough time was allowed for the excess magnesium to react with the acid. The product was extracted with benzene, and washed with dilute sodium hydroxide solution and water. The solution of organic substances was dried over anhydrous magnesium sulfate.

The dried solution was filtered, and the solvent was evaporated under reduced pressure, and the residue was vacuum distilled. The main fraction was obtained at 100-108° and 0.5 mm (lit. bp 140-142° at 10 mm). The yield of the product, which was a low melting solid, was 33.8 g (71.5%) based on 2-chlorocyclopentanone.

M. 5-Hydroxymethylene-2-phenylcyclopentanone

Sodium methoxide (0.2 mole) was obtained from 4.6 g of sodium metal and 60 ml of absolute methanol. The solvent was evaporated, and the sodium methoxide was dried thoroughly at 200° and 2 mm for 2 hours. It became powdered by shaking the flask. Ethyl formate was dried over anhydrous magnesium sulfate and freshly distilled for the following
reaction.

To the ice-cold suspension of sodium methoxide in benzene (200 ml) were added with swirling 2-phenylcyclopentanone (16.0 g, 0.10 mole) and ethyl formate (14.8 g, 0.20 mole). The mixture turned orange and the solid product appeared. Occasional shaking was applied and the reaction mixture was kept under nitrogen while allowed to stand at room temperature overnight.

Ice water was added, the aqueous layer was separated, and the benzene solution was washed thoroughly with cold dilute hydrochloric acid. All of the aqueous solutions were combined, washed once with ether, and acidified with dilute hydrochloric acid. Then, the solution was extracted several times with ether. The ether extract was washed with ice water and dried over anhydrous magnesium sulfate. The crude product appeared as a brown, viscous oil which amounted to 90-100% yield. The product did not crystallize, and was used for the following reaction as soon as it was prepared.

N. 3-Cyano-7-phenyl-1,5,6,7-tetrahydro-2H-1-pyrindin-2-one
(48)22-24

A sample of 5-hydroxymethylene-2-phenylcyclopentanone (19.5 g, 0.103 mole) was dissolved in 220 ml of absolute ethanol by warming. The solution was cooled, and 2-cyanoacetamide (12.6 g, 0.150 mole) was added with stirring, followed by 7 ml of triethylamine. The mixture was refluxed for 6 hours under nitrogen and dry conditions. A magnetic stirrer
was used. The resulting dark brown solution was put in the refrigerator overnight. The product was recrystallized from absolute ethanol. The yield of pure product (mp 229-230°) was 4.33 g (17.7% yield). The product gave a purple fluorescence in solution.

The infrared spectrum of the product showed the following characteristics: 3390 (broad, w, N-H), 2212 (sharp, m, C=N), and three strong absorptions at 1639, 1592 and 1567 cm⁻¹ (2-pyridone). The spectrum is shown in Fig. 15.


0. 3-Carboxy-7-phenyl-1,5,6,7-tetrahydro-2H-1-pyrindin-2-one (49)²⁵

The cyanide 48 (3.86 g) was refluxed with 40 ml of concentrated sulfuric acid and 40 ml of water under nitrogen with stirring for 5 hours. The solution was cooled, and a large volume of ice water was added, to a total volume of 400 ml. A white colloidal material appeared. The flask was cooled in ice for 5 hours, and the precipitate was filtered. The product was washed thoroughly with water to get rid of sulfuric acid, pressed dry under suction, and dried over sodium hydroxide pellets. The yield was 3.82 g (92%).

After five recrystallizations from absolute ethanol, white crystals were obtained. The compound gave a purple fluorescence in ethanol and acetone solutions. It melted at
Fig. 15. (Upper) Infrared Spectrum of 3-Cyano-7-phenyl-1,5,6,7-tetrahydro-2H-1-pyrindin-2-one.

Fig. 16. (Lower) Infrared Spectrum of 7-phenyl-1,5,6,7-tetrahydro-2H-1-pyrindin-2-one.
250-251° with decomposition and evolution of a gas, presumably carbon dioxide.

The infrared spectrum showed the following characteristic peaks: 3390 (broad, w, N-H), 2500-3000 (broad, m, CO$_2$H), 1712 (s, C=O of CO$_2$H), and three strong bands at 1634, 1592, and 1548 cm$^{-1}$ (2-pyridone).

Anal. Calcd for C$_{15}$H$_{13}$NO$_3$ (mol wt=255.3): C, 70.58; H, 5.13; N, 5.49. Found: C, 70.11, 70.12; H, 5.36, 5.37; N, 5.37, 5.41.

P. 7-Phenyl-1,5,6,7-tetrahydro-2H-1-pyrindin-2-one (47)

The carboxylic acid 49 (2.0 g) was placed in a 3-necked flask with 45 ml of light liquid paraffin. While raising the temperature slowly, the mixture was stirred, and nitrogen was kept sweeping through the flask. When the temperature reached about 240°, a gas was evolved, and most of the gas was gone before 245°. The temperature was raised and kept at 290-310° for 15 minutes. The flask was allowed to cool thoroughly to room temperature. The product was filtered from the white viscous liquid and was washed with low boiling petroleum ether (bp 30-60°). Recrystallization from ethanol gave 1.21 g of product (73.5%), with mp 169-176°. After several more recrystallizations, white crystals, which melted at 177-179°, were obtained. This compound also gave a purple fluorescence in solution.

The infrared spectrum showed the following characteristic absorptions: 3400 (broad, w, N-H), and three strong bands
at 1647, 1605, and 1553 cm\(^{-1}\) (2-pyridone). The infrared spectrum is shown in Fig. 16.

The ultraviolet spectrum gave maxima at 235 m\(\mu\) (\(\varepsilon\) 6430) and 320 (8970). It is shown in Fig. 17.

The nmr spectrum (100 Mc, CDCl\(_3\)) showed peaks at \(\delta\) 2.12 (multiplet, C-6 methylene protons), 2.73 (multiplet, C-5 methylene), 4.18 (triplet, \(J=6.5\) cps, C-7 proton), 6.27 (doublet, \(J=9\) cps, C-4 proton), 7.15 (multiplet, phenyl protons), 7.33 ppm (doublet, \(J=9\) cps, C-3 proton). The N-H peak was detected to appear at \(\delta\) 9.36 with DMSO-\(d_6\) solution sample, and was not observed with CDCl\(_3\) solution sample. The \(\delta\) 2.73 peak probably contained resonance of an impurity. The nmr spectrum is shown in Fig. 18.

The mass spectrum showed peaks at m/e 211 (molecular ion and base peak) and 134 (16\%) in addition to other fragments of low intensities.

**Anal. Calcd for C\(_{14}\)H\(_{13}\)NO (mol wt=211.3):** C, 79.59; H, 6.20; N, 6.63. **Found:** C, 79.58, 79.74; H, 6.27, 6.35; N, 6.53, 6.58.
Fig. 17. Ultraviolet Spectrum of 7-Phenyl-1,5,6,7-tetrahydro-2H-1-pyrindin-2-one in 95% Ethanol.
Fig. 18. Nmr Spectrum of 7-Phenyl-1,5,6,7-tetrahydro-2H-1-pyrindin-2-one in CDCl₃.
III. DISCUSSION AND RESULTS

A. Evaluation of Oxazine 1 as the Structure of the Condensation Product

Stetter and Hoehne\(^1\) reported that the compound obtained from \(\beta\)-nitrostyrene and 1,3-cyclohexanedione, in the presence of sodium methoxide, was not a normal Michael addition product. By elemental analysis, they found that the product was a 1:1 molar adduct with subsequent elimination of a molecule of water, and the oxazine 1 was proposed as the structure. They also reported that hydrogenation of 1 over Raney nickel catalyst provided 3, which in turn was dehydrogenated to form 4. Further, hydrolysis of 1 gave keto acid 5, from which 2-phenyloctanedioic acid was obtained through Wolff-Kishner reduction.\(^1\)

\[\text{Raney nickel catalyst provided 3, which in turn was dehydrogenated to form 4. Further, hydrolysis of 1 gave keto acid 5, from which 2-phenyloctanedioic acid was obtained through Wolff-Kishner reduction.}\]
There were no spectral data to support the structure 1. Besides, oxazine 1 is also a nitronic ester; and nitronic esters are not available from the reaction of a nitro group and alcohol or enol as in the present reaction.\textsuperscript{26a} Reported methods\textsuperscript{26a} from which nitronic esters have been obtained are: (1) the reaction of nitro compounds with diazomethane, (2) alkylation of alkali metal salts of nitro compounds, (3) treatment of the silver salts of nitro compounds with alkyl iodides, and (4) reaction of the salts of nitroparaffins with trialkyloxonium fluoroborates. Thus, structure 1 and the reaction leading to it is implausible.

With the structure of 1 in doubt, the structure of 2 and 4 were not secure, but in the final analysis, quite surprising to us, structures 3 and 4 were proved to be correct.

B. Discussion of Experimental Results

1. \textit{N-Hydroxy-3-phenyl-4,5,6,7-tetrahydrooxindol-4-one}

(6)

The condensation product of 1,3-cyclohexanedicarboxylic acid and \(\beta\)-nitrostyrene was a 1:1 molar adduct with subsequent elimination of a molecule of water. The elemental analysis and the molecular ion peak of the mass spectrum confirmed this.

A preliminary observation of the compound showed that in the infrared spectrum, there were a strong hydroxyl band at 3333 cm\(^{-1}\) and two carbonyl stretching bands at 1698 and 1631 cm\(^{-1}\). The compound gave a positive ferric chloride test,\textsuperscript{7} which indicated the presence of a N-OH group. As is known, a
primary nitro group can be converted into an aldehyde, carboxylic acid, or hydroxamic acid under various conditions.\textsuperscript{26b} In view of these, we proposed the cyclic hydroxamic acid $6$ for the structure of the product.

\begin{center}
\textbf{6}
\end{center}

Compound 6 hydrolyzed to keto acid $5$, which was converted, through a Wolff-Kishner reduction, into 2-phenylpicotanedioic acid.\textsuperscript{1} The dibasic acid had the same melting point as an authentic sample prepared later, by another research group, by an established method of synthesis.\textsuperscript{3} The keto acid and the dibasic acid confirmed the location of a second carbonyl group at C-2 position in structure 6. The hydrolysis of 6 was analogous to that of other vinylogous imides,\textsuperscript{27,28} through the following sequence:
The two infrared bands (Fig. 1) at 1698 and 1631 cm\(^{-1}\) are characteristic of vinylogous imide carbonyls. It is known\(^{29,30}\) that the C-2 carbonyl group of \(\gamma\)-lactams absorbs at around 1700 cm\(^{-1}\). For comparison, 3-phenyloxindole was synthesized and its carbonyl stretching was found to appear at 1701 cm\(^{-1}\). Noland\(^{31}\) also reported a series of \(\gamma\)-lactams and N-hydroxy-\(\gamma\)-lactam 7 in which the carbonyl absorptions occurred at close to 1700 cm\(^{-1}\). On the other hand, compounds 3 and 4 (which will be discussed later) showed that their C-4 carbonyls appeared at frequencies as low as 1582 and 1631 cm\(^{-1}\) respectively. So, it seemed reasonable to assign the 1698 and 1631 cm\(^{-1}\) bands of 6 to C-2 and C-4 carbonyl groups respectively. Values of the two carbonyl stretching frequencies of the following vinylogous imides had been reported:

- Compound 8, 1700 and 1640 cm\(^{-1}\);\(^{32}\)
- Compound 9, 1700 and 1650 cm\(^{-1}\);\(^{32}\)
- Compound 10, 1695 and 1645 cm\(^{-1}\);\(^{33}\)
- Compound 11, 1696 and 1622 cm\(^{-1}\);\(^{34}\)
- Compound 12, 1690 and 1650 cm\(^{-1}\).\(^{34}\)
The ultraviolet spectrum of 8 (Fig. 2) exhibited a maximum at 268 m\(\mu\) (\(\varepsilon 10,250\)). This agreed with those of some related vinylogous imides: 8, 288 m\(\mu\) (\(\varepsilon 10,300\)); 10, 298 m\(\mu\) (\(\varepsilon 12,600\)); 11, 280 m\(\mu\) (\(\varepsilon 27,300\)); and 12, 281 m\(\mu\) (\(\varepsilon 27,200\)).

The large peak at \(\delta 7.24\) ppm of the nmr spectrum of 8 (Fig. 3) was due to the phenyl protons. The three high-field multiplets, at \(\delta 2.03, 2.21,\) and 2.69 were due to the C-6, C-5, and C-7 methylene protons respectively. Certainly, among the three methylene groups, the C-6 methylene protons would be expected to appear at the highest field. By spin decoupling study, it was found that the protons corresponding to \(\delta 2.69\) coupled with C-3 proton at 4.98 (triplet, \(J=2.0\) cps). Since coupling between C-5 protons and C-3 proton was unlikely, and homoallylic coupling could occur between C-7 protons and C-3 proton, the \(\delta 2.69\) peak was assigned to C-7 protons. The homoallylic coupling constant was in agreement with the literature data. The sharp singlet at \(\delta 10.20\) was assigned to the N-OH proton resonance.
2. **N-Acetoxy-3-phenyl-4,5,6,7-tetrahydrooxindol-4-one (13)**

N-Hydroxy-3-phenyl-4,5,6,7-tetrahydrooxindol-4-one (6) was converted into its acetyl derivative 13. Comparison of the infrared spectra of 6 and 13 showed that the hydroxyl band of 6 at 3333 cm\(^{-1}\) had been converted into an acetoxy carbonyl band of 13 at 1761 cm\(^{-1}\). (Fig. 4) The two carbonyl bands of the vinylogous imide system were retained, but with a slight shift to 1681 and 1653 cm\(^{-1}\). The acetoxy carbonyl band critically ruled out structure 14 as an alternative structure for 13. This in turn ruled out 14 as an alternative structure for 6. On the other hand, the presence of the C-2 carbonyl band ruled out the possibility of enolization of the C-2 carbonyl and subsequent acetylation of the enol.

In the nmr spectrum of the acetyl derivative 13 (Fig. 5), the phenyl protons and the C-6, C-5, and C-7 methylene protons showed up at the chemical shifts comparable to those of compound 6. The acetyl derivative was a monoacetate as shown by elemental analysis. However, the resonance of the acetyl
protons appeared as two singlets at $\delta$ 1.82 and 2.12 ppm with the concomitant appearance of two C-3 triplets ($J=2.3$ cps) at $\delta$ 5.01 and 5.10. By spin decoupling, it was established that both the $\delta$ 5.01 and 5.10 peaks coupled with C-7 protons at $\delta$ 2.71. It was assumed, though not proved, that there was a restriction to the rotation of the N-O bond,\textsuperscript{36} that lead to two conformers with the acetyl groups in different environments. The two C-3 triplets would arise from the influence of the acetyl groups in different environments.

3. 3-Phenyl-2,3,4,5,6,7-hexahydroindol-4-one (3)

Reduction of N-hydroxy-3-phenyl-4,5,6,7-tetrahydrooxindol-4-one (6), with hydrogen and Raney nickel, afforded compound 3.

\[ \text{Hydrogenolysis of the N-hydroxyl group was involved in the reduction. This was easily followed by the infrared and nmr spectra. The hydrogenolysis was in agreement with comparable transformations reported by Noland and coworker,}^{31} \text{ such as the following two reactions:} \]
From the above information, the elemental analysis, and the molecular weight from the mass spectrum of 3, it was clear that one of the two carbonyl groups had been reduced to a methylene group. Based on the spectral data of 3, and its dehydrogenated derivative 4 (which will be discussed later), we concluded that it was the C-2 carbonyl group that had been reduced. Vinylogous amide 16 was resistant to reduction by hydrogen and Raney nickel,\textsuperscript{11} so the survival of C-4 carbonyl of 3 under this condition was plausible. However,
conversion of the C-2 carbonyl group to a methylene group with hydrogen and Raney nickel was an exceptional case, since the survival of lactams under this condition had been amply demonstrated.\textsuperscript{22,31}

Vinylogous amides had been reported\textsuperscript{11-15} to give a positive ferric chloride color test. The color produced varied from red, pink, purple, to blue. For compound \textsuperscript{3}, an immediate pink color was obtained.

Like other vinylogous amides, the infrared spectrum of compound \textsuperscript{3} (Fig. 6) was unusual. The normal carbonyl stretching vibration of unconjugated ketones was found quite consistently at 1705-1725 cm\textsuperscript{-1}, and that of \(\alpha,\beta\)-unsaturated ketones, including aryl ketones, was found at 1665-1700 cm\textsuperscript{-1}.\textsuperscript{12} However, Cromwell and coworkers,\textsuperscript{12} from a study of a series of vinylogous amides (\(\beta\)-amino-\(\alpha,\beta\)-unsaturated ketones) in the solid state, observed that their carbonyl bands were lowered by 20-80 cm\textsuperscript{-1} from those of the parent \(\alpha,\beta\)-unsaturated ketones. Thus, the carbonyl bands of some of these compounds appeared at a frequency as low as 1600 cm\textsuperscript{-1} or lower. They concluded that the substitution of an amino group at the beta position of these \(\alpha,\beta\)-unsaturated ketones lowered the carbonyl frequency,\textsuperscript{12} through the \(\pi\)-p conjugation interaction between the two parts.\textsuperscript{15,34}

The carbonyl absorption frequencies in the infrared spectra of some vinylogous amides were reported to be: compound 16, 1626 cm\textsuperscript{-1};\textsuperscript{11} 17, 1602 cm\textsuperscript{-1};\textsuperscript{12} 18, 1590 cm\textsuperscript{-1};\textsuperscript{12} 19, 1598 cm\textsuperscript{-1};\textsuperscript{12} 20, 1619 cm\textsuperscript{-1};\textsuperscript{37} 21, 1607 cm\textsuperscript{-1};\textsuperscript{37} and
According to the literature,\textsuperscript{11-14} in the infrared spectra of the vinylogous amides, there is no absorption in the region 1700-1800 cm\textsuperscript{-1}. The region of interest is 1500-1700 cm\textsuperscript{-1}. In this region, absorptions due to C=O, C=C, C=N, N-H,
and phenyl can appear. It has been pointed out that assignments of bands should be tentative.\textsuperscript{16,38} However, it has been generally accepted that the band at the highest frequency in this region could be assigned to the carbonyl absorption, although it might not be the strongest absorption in this region.\textsuperscript{12,16,37}

In the infrared spectrum of compound 3, there was no band in the 1600-1800 cm\textsuperscript{-1} region. The highest frequency band in the 1500-1800 cm\textsuperscript{-1} region was 1582 cm\textsuperscript{-1}; there were two more bands, 1555 and 1508-1527 (broad) cm\textsuperscript{-1}, in this region. Although the broad band at 1508-1527 cm\textsuperscript{-1} was stronger than the 1582 band, theoretically the latter should be due to the carbonyl group. Since assignments of other bands were not definite,\textsuperscript{12,16,38} no such attempt was made.

The ultraviolet spectrum of 3 (Fig. 7) showed maximum absorption at 308 m\textsuperscript{\mu} (\epsilon 21,600). This agreed with the literature data: compound 16, 303 m\textsuperscript{\mu} (\epsilon 30,200);\textsuperscript{11} 24, 308 m\textsuperscript{\mu} (\epsilon 18,400);\textsuperscript{12} 25, 306 m\textsuperscript{\mu} (\epsilon 22,800);\textsuperscript{12} and 26, 314 m\textsuperscript{\mu} (\epsilon 16,600).\textsuperscript{14} The spectrum of 3 did not show any change in

\begin{align*}
\text{CH}_3-C-\text{CH}=\text{C(CH}_3\text{)-NH-CH}_2\text{CH}_2\text{CN} \\
\text{24}
\end{align*}

\begin{align*}
\text{CH}_3-C-\text{CH}=\text{C(CH}_3\text{)-N(CH}_3\text{)-CH}_2\text{CH}_2\text{CN} \\
\text{25}
\end{align*}
wavelength or intensity in base, whereas in acid, there was a considerable hypsochromic shift and a decrease in intensity. These properties were consistent with those of some other vinylogous amides reported,\textsuperscript{13,16} such as compounds \textsuperscript{22} and \textsuperscript{23}.\textsuperscript{16}

In the nmr spectrum of \( \mathbf{3} \), (Fig. 8) the phenyl protons at \( \delta 7.15 \) ppm showed that the phenyl group was not reduced when \( \mathbf{6} \) was converted into \( \mathbf{3} \). The six-membered ring was also unchanged. The C-6 methylene protons appeared as a highest-field multiplet centered around \( \delta 1.95 \), whereas the C-5 and C-7 methylene protons appeared as another multiplet, twice as intense, centered around \( \delta 2.23 \). The N-H resonance occurred as a broad singlet at \( \delta 6.35 \). When the solvent was changed from CDCl\(_3\) to DMSO-d\(_6\), this peak shifted downfield to \( \delta 7.31 \).

The three protons, of AMX pattern, were assigned to C-2 and C-3 protons. Among these, \( H_A \) probably appeared at the highest field. Based on this and the fact\textsuperscript{39} that \( J_{\text{trans}} \) in a planar five-membered ring is much smaller than \( J_{\text{cis}} \), the individual protons were assigned as followed: \( H_A \) at \( \delta 3.29 \)
The sum of the coupling constants, \( J_{\text{cis}} \) and \( J_{\text{trans}} \), was 16 cps, which was comparable to those observed for 28, 29 and 30 (17.0, 18.4, and 16 cps respectively). The \( J_{\text{gem}} \) of the C-2 protons of pyrrolidine was reported to be 9.5 cps; and the two \( J_{\text{vic}} \) of compound 31 were 5.5 and 9 cps.

The keto-imine 3a and the enol-imine 3b, which are tautomers of the keto-enamine 3, have not been unambiguously ruled out by the above discussion.

With isolated chromophores, 3a could not exhibit the observed ultraviolet spectrum. Besides, in the infrared
spectrum, it should give a normal carbonyl band at around 1705-1725 cm\(^{-1}\) and no band in higher frequency region than the C-H stretching region. In the nmr spectrum, the additional tertiary C-H should cause further spin-spin splitting of the observed AMX pattern for the C-2 and C-3 protons. These would be contradictory to what actually was observed. Thus, 3a could not be the structure.

Structures 3 and 3b could not be distinguished unambiguously by nmr spectrum, since it is known that N-H may\(^42,43\) or may not\(^44\) couple with the proton or protons on the adjacent carbon. However, the ultraviolet spectrum in base,\(^13,16\) which did not show a shift in wavelength, indicated that 3b would have been a poor choice. Available literature information, which will be discussed below, supported the choice of structure 3.

By studying the infrared spectra of various vinylogous amides, Cromwell and coworkers,\(^12\) and Weinstein and Wyman\(^13\) proved that they were keto-enamines, probably chelated through intramolecular hydrogen bonds. More recently, Cromwell and David\(^16\) studied two bicyclic vinylogous amides, 22 and 23, by infrared and ultraviolet spectra, they concluded that the
compounds were keto-enamines. These two compounds are closely related to compound $\equiv$ in the location of vinylogous amide moiety.

Nmr spectra reported in the literature also gave strong support to this. Dudek and Holm$^{42}$ reported a system where an enol-imine tautomer might be of comparable stability. They observed that the benzylic methylene protons of compound $\equiv$ appeared as a doublet at $\delta$ 4.67 ($J=4.8$ cps), which collapsed to a singlet upon deuteration of the acidic proton. Compound 33 exhibited a similar spectral property. In both compounds, the stability of the keto-enamine form with its chelated hydrogen-bonded ring was found sufficient to destroy the aromatic structure of one of the naphthalene rings. They concluded that at least 95% of the compounds existed as the keto-enamine form. This was strong evidence for the preferable keto-enamine form.

So far, the origin of the unusually low carbonyl frequency in the infrared spectrum of $\equiv$ has not been accounted for. Intramolecular hydrogen bonding,$^{12,13,42,45}$ intermolecular
hydrogen bonding, and resonance structure contribution have been used to explain the anomaly. Intramolecular hydrogen bonding is not possible in compound \( \equiv \), which is a rigid, planar system. Intermolecular hydrogen bonding seems to be present judging from the N–H stretching frequency. However, the large carbonyl shift implies that the ionic structure form must contribute appreciably to the ground state. This resonance form arises from the \( \pi-p \) conjugation interaction through the insertion of a vinyl linkage. The ground state is reflected in its infrared spectrum shift and the altered functional group character.

Compound failed to give usual carbonyl derivatives, such as semicarbazone, tosylhydrazone, and 2,4-dinitrophenylhydrazone. It had been reported that vinylogous amides behave chemically more like amides than ketones, and do not give usual ketone derivatives.

4. 3-Phenyl-4,5,6,7-tetrahydroindol-4-one (4)

3-Phenyl-2,3,4,5,6,7-hexahydroindol-4-one (3) was dehydrogenated with Raney nickel in hot ethanol to form
compound \( \frac{4}{4} \). The ease of the transformation, \( C_{14}H_{15}NO \rightarrow C_{14}H_{13}NO \), suggested that an aromatic system had been generated.

\[
\begin{align*}
\text{R} = \text{H} \\
\text{R} = \text{CH}_3
\end{align*}
\]

Compound \( \frac{4}{4} \) was by far the most stable compound in the series of transformations: \( \frac{6}{6} + \frac{3}{3} \rightarrow \frac{4}{4} \).

In the infrared spectrum of compound \( \frac{4}{4} \) (Fig. 9), the 3185 cm\(^{-1}\) band was attributed to the N-H stretching. The strong band at 1631 cm\(^{-1}\) should be assigned to the C-4 carbonyl. The low frequency of a carbonyl group conjugated with a pyrrole ring had been reported, for instances, those of 35 and 36 were at 1617 and 1646 cm\(^{-1}\) respectively.\(^{46}\)

The ultraviolet spectrum of compound \( \frac{4}{4} \) (Fig. 10), showed maxima at: 218 m\(\mu\) (\(\epsilon \, 22,080\)), 242 (shoulder, 8450), 263
(10,400), and 287 (shoulder, 6570).

In the nmr spectrum of 4 (Fig. 11), the multiplet at δ 2.04 ppm, and the triplets (J=6 cps) at δ 2.36 and 2.80 were due to the C-6, C-5, and C-7 methylene protons respectively. The doublet at δ 6.91 (J=2.5 cps) was due to the C-2 proton of the pyrrole ring. The phenyl protons appeared as two multiplets at δ 7.23 and 7.62. The N-H resonance was a broad singlet at δ 11.48. The most important difference between the nmr spectrum of compound 4 and that of 3 was that the AMX pattern of signals (due to C-2 and C-3 protons) of 3 had been converted into a doublet at δ 6.91 (due to the C-2 proton) in 4.

Raney nickel is known to promote dimerization. 49 For compound 4, however, the molecular weight obtained from the mass spectrum and the clean nmr spectrum obviated this consideration.

5. Authentic Sample of 3-Phenyl-4,5,6,7-tetrahydroindol-4-one (4)

It was pointed out earlier that the removal of the C-2 carbonyl group by reduction of 6 to form 2, with Raney nickel and hydrogen, was unexpected. Synthesis of 4 by an independent method would establish the skeleton for compounds 6, 3, and 4, as well as prove the structure for 4.

There are several methods 17,50 for the synthesis of 4,5,6,7-tetrahydroindol-4-ones. The method developed by Schoen and Pachter 17 was adopted because of its simplicity and
the particular substitution feature of the required compound 4.

In the synthesis, ethyl benzoyleacetate was converted into its nitroso derivative through the reaction of nitrous acid on the active methylene group. The secondary nitroso compound was unstable and readily isomerized to the oximino derivative which was a yellow solid. After the condensation with 1,3-cyclohexanedione, the adduct was reduced to an amine with zinc and acetic acid, cyclized, and dehydrated to compound 37.

Compound 37 showed characteristic infrared bands (Fig. 12) of N-H at 3165 cm⁻¹, ester carbonyl at 1689 cm⁻¹, and C-4 carbonyl at 1639 cm⁻¹. It was analyzed as the high melting
(275-277°) semicarbazone derivative which contained characteristic functional groups as shown in the infrared spectrum.

Carboxylic acid 38 was obtained by hydrolyzing the ester 37 in aqueous sodium hydroxide solution. The two carbonyl groups of 38 appeared as a broad band centered around 1637 cm\(^{-1}\). The acid was also recognized by its broad absorption band at 2500-3333 cm\(^{-1}\).

The authentic sample of compound 4 was obtained by decarboxylation of 38. The carbonyl band at 1631 cm\(^{-1}\), the N-H band at 3185 cm\(^{-1}\), and other infrared absorptions of this sample (Fig. 13) were identical with those of 4 obtained from the method by Stetter and Hoehne.\(^1\)

The two samples of compound 4, from different routes, gave identical melting point at 238-239°. Their mixture melting point was also 238-239°. Their mass spectra were identical. Further, their nmr spectra (Fig. 11 and 14) were essentially identical, with only very slight deviations in chemical shifts presumably due to different concentrations of the nmr sample solutions.

6. Conclusion

With structures of 6 and its acetyl derivative 13 fully elucidated, we concluded that the reaction of \(\beta\)-nitrostyrene and 1,3-cyclohexanedione produced the vinylogous imide 6, but not the oxazine 1 as proposed by Stetter and Hoehne.\(^1\) The structures of other two derivatives 2 and 4, also proposed by Stetter and Hoehne, incidentally were correct.
C. Relationship Between the Condensation Reaction and General Reactions of Nitro Group

Conversion of primary or secondary nitro compounds, or their salts, with strong acid, into carbonyl compounds has long been known. A primary nitro compound, for instance, when boiled with strong mineral acid gives a hydroxamic acid, which is then hydrolyzed to carboxylic acid and a salt of hydroxylamine. In the Nef reaction, a salt of a primary or secondary nitro compound is converted into an aldehyde or ketone respectively, when hydrolyzed with acid. Under certain conditions, small amounts of carboxylic acid and hydroxylamine salt or hydroxamic acid have been isolated from the Nef reaction.

3-Nitrocamphor has been reported to rearrange to a N-substituted imide with acid. A similar rearrangement has also been observed for α-nitroketone in steroid molecules,

![Chemical structures](image)

such as 39. More recently, Turner reported the conversion of 40 into 41. These reactions involve the rearrangement of a secondary nitro group to a hydroxamic acid derivative.
All the reactions discussed above involve acidic medium. Reaction of primary nitroalkanes with alkali is complex. This has been illustrated by the decomposition of 2-phenylnitroethane by sodium hydroxide to six isolated products and several unidentified compounds. Condensation of cyclohexanone and nitromethane, in the presence of secondary amines, to form the lactam $\mathcal{Z}$, involved a conversion of a primary nitro group into a cyclic hydroxamic acid.

The conversion of a primary nitro group with sodium methoxide into a hydroxamic acid group, in the present research, is reported the first time. The ease of the reaction which takes place at the room temperature is also unique. In the course of the condensation, the adduct $\mathcal{Z}$, a nitronic acid or its
tautomer, is presumably converted into 43 which is a plausible predecessor of 6. The transference of an oxygen atom from nitrogen to carbon under this nonaqueous medium imples that a small ring intermediate, the oxaziran 44, may be involved.55

\[
R-\text{CH}_2\text{NO}_2 + R-\text{CH}_2-\text{NOH} \rightarrow R\text{-C}-\text{N}-\text{OH} + R\text{-C}-\text{NH}_2\text{OH}
\]

D. An Incorrect Hypothesis 4

As a working hypothesis, the following sequence of reactions was used for an earlier interpretation for Stetter and Hoehne's work. Structure 45 was thought to be the correct
reassignment for compound 1 because the ultraviolet spectrum would compare favorably with 3-phenylcyclopentenone, and the infrared spectrum seemed to fit a cyclopentenone and δ-lactam. At the same time, structures 46 and 47 were reassigned for compounds 3 and 4, respectively.

Compound 47 was synthesized from an alternative route to test the above hypothesis. The synthesis began with the coupling of 2-chlorocyclopentanone with phenylmagnesium bromide according to the procedure of Mislow and Hamermesh,18 and then followed the following sequence. The hydroxymethylene derivative was prepared according to the procedures of Johnson and Posvic.20 This derivative was oxidized rapidly in air, but its condensation with 2-cyanoacetamide according to a known method22-24 gave 48. Compound 48 was hydrolyzed to the
carboxylic acid 49, and then decarboxylated to the pyrindinone 47.

In the ethyl formate reaction step, the substitution occurred at C-5 position, which was consistent with several precedences.18,20,21 The product 48 obtained from the next condensation step also indicated this position of substitution.

Absolute ethanol was found to be a better solvent than benzene for the 2-cyanoacetamide condensation step, since 2-cyanoacetamide is solubile in ethanol but not in benzene. Triethylamine was also a better choice than pyridine or piperidine as a base.

The conversions, 48 + 49 + 47, could be followed easily by the infrared spectra of the compounds. The cyano derivative 48 showed a sharp C≡N band at 2212 cm⁻¹ (Fig. 15). After
hydrolysis, the carboxylic acid 49 was formed, which was indicated by a strong carbonyl absorption at 1712 cm\(^{-1}\). The broad band, with medium intensity, extended from 2500 cm\(^{-1}\) to the C-H stretching region, also proved the carboxylic acid group. The 1712 cm\(^{-1}\) band was removed upon decarboxylation to 47 (Fig. 16). Each of the three compounds had three strong absorptions in the 1538-1667 cm\(^{-1}\) region, characteristic of a 2-pyridone ring: 56-59 compound 48, 1639, 1592, and 1567 cm\(^{-1}\); 49, 1634, 1592, and 1548 cm\(^{-1}\); and 47, 1647, 1605, and 1553 cm\(^{-1}\).

Structure 47 was also supported by the ultraviolet, nmr, and mass spectra. Its ultraviolet spectrum (Fig. 17) had two maxima at 235 nm (\(\varepsilon\ 6430\)) and 320 (8970). These values agreed with those known for 2-pyridones. 56-58, 60 The ultraviolet maxima for \(\beta\)-obscurine (50) were at 232 nm (\(\varepsilon\ 9550\)) and 315 (7760); 56, 58 6-methyl-2-pyridone at 229 nm (\(\varepsilon\ 7410\)) and 304 (6760); 58 and selagine (51) at 231 nm (\(\varepsilon\ 10,700\)) and 313 (8500). 57
In the nmr spectrum (Fig. 18) of 47, the four aliphatic protons appeared as two multiplets at the high field. A triplet at δ 4.18 ppm, with a coupling constant of 6.5 cps, was attributed to the benzylic proton. The phenyl protons appeared at δ 7.15 as a multiplet. An AB quartet with a coupling constant of 9 cps was assigned to the protons on the 2-pyridone ring; the higher-field doublet centered around δ 6.27 was due to the C-4 proton, and the lower-field doublet centered around δ 7.33 was due to the C-3 proton. These values agreed with those in the literature. The AB quartet of 8-obscurine was at δ 6.37 and 7.79 with J = 10 cps, and that of compound 52 was at δ 6.62 and 7.96. The N-H of compound 47 appeared as a broad singlet at δ 9.36. The mass spectrum confirmed the molecular weight, which corresponded to the most intense peak at m/e 211. The m/e 134 peak resulted from the fragmentation of a phenyl fragment.

After the sample of 47 had been synthesized, its melting point was found to be 60° lower than that of 4. The ultraviolet spectrum of 4 was completely different from that of 47 and those of other 2-pyridones in the literature. Characteristic infrared bands of 2-pyridones in the 1538-1667 cm⁻¹ region were not found in 4. Further, the AB quartet, typical for the nmr spectra of 5,6-substituted 2-pyridones, was not present. The mass spectra of 4 and 47 were different. And, 4 did not give any fluorescence in solution whereas 47 gave a strong purple fluorescence in solution; another 2-pyridone had also been reported to give a
strong yellow-green fluorescence. After knowing that the structure did not agree with compound, we abandoned the hypothesis, and turned our attention to another hypothesis and the synthesis of the authentic sample of 3-phenyl-4,5,6,7-tetrahydroindol-4-one (4).
IV. CONCLUSION

Condensation of α-nitrostyrene with 1,3-cyclohexanedione in the presence of sodium methoxide did not yield a normal Michael addition product. The product was proved to have structure 6. The acetyl derivative 13, which gave strong support to structure 6, was prepared. The acetoxy carbonyl band in the infrared spectrum of 13 unambiguously ruled out its isomeric structure 15. This in turn ruled out the isomeric structure 14 as an alternative structure for 6.

Upon hydrolysis, compound 6 could be converted into keto acid 5, from which a known compound, 2-phenyloctanedioic acid, could be obtained through Wolff-Kishner reduction. Hydrogenation of 6 over Raney nickel catalyst produced 3, which was then dehydrogenated with Raney nickel in hot ethanol to form 4. Structures 3 and 4 were fully elucidated, and an authentic sample of 4 was synthesized.
Stetter and Hoehne proposed oxazine 1 as the structure of the condensation product. Our research concluded that this proposal was wrong, and the structure should be reassigned as 6. Unexpectedly, we found that compounds 3 and 4 agreed with the structures which were also proposed by them.

In the course of the condensation, the adduct 42, a nitronic acid or its tautomer, was presumably converted into 43, which was a plausible predecessor of 6. The transference of an oxygen atom from nitrogen to carbon, under nonaqueous
medium, implied that a small ring intermediate, the oxazine 44, might be involved.

The conversion of a primary nitro group, in the presence of sodium methoxide, into a hydroxamic acid group, found in this research, was the first case observed. The ease of the reaction, which took place at room temperature was also unique. In addition, hydrogenation of 6 to form 3, involved catalytic reduction of the carbonyl group of a cyclic amide to a methylene group which has seldom been observed.
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